Drug Class Review

Newer Diabetes Medications and Combinations

Final Update 2 Report

July 2016

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STRUCTURED ABSTRACT

Purpose

To compare the effectiveness and adverse event profiles of DPP-4 inhibitors, GLP-1 analogs, SGLT2 inhibitors, and certain drug combinations (administered as dual therapy or fixed dose combination products) for people with type 2 diabetes.

Data Sources

To identify published studies, Ovid MEDLINE®, the Cochrane Database of Systematic Reviews®, and the Cochrane Central Register of Controlled Trials® through February Week 1 2016. We also reviewed reference lists of recent systematic reviews for studies that our electronic searches may have missed and we requested relevant information from pharmaceutical manufacturers.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project methods. For this streamlined update report, we included only head-to-head comparisons of newer diabetes drugs (and combinations) and comparisons of newer diabetes drugs with metformin.

Results

We identified 52 studies including 43 trials (22 this update) and 5 companion publications (4 this update), 3 observational studies (all this update), and 1 systematic review (this update). All trials enrolled adults with type 2 diabetes mellitus and evaluated intermediate outcomes, such as changes in HbA1c and weight. Long-term health outcomes (e.g., death, myocardial infarction, cerebral vascular accident) were incidentally reported in trials and were rare enough that no meaningful conclusions could be drawn from the evidence. We also had few observational studies of harms that met inclusion criteria.

Ten trials compared two medications of the same class. There was moderate-strength evidence that exenatide XR reduced HbA1c from baseline more than exenatide and low-strength evidence that liraglutide and dulaglutide decreased HbA1c more than exenatide. Albiglutide and higher-dose dulaglutide reduced weight more than exenatide. However, there was greater weight loss with liraglutide than either albiglutide or dulaglutide, and liraglutide was also associated with a greater proportion of patients achieving an HbA1c <7% than albiglutide.

There were 17 trials that compared 1 drug class with another; all comparisons were made against a DPP-4 inhibitor. The 9 trials that compared a GLP-1 analog with a DPP-4 inhibitor provided low strength evidence that exenatide XR, albiglutide, dulaglutide, and liraglutide reduced HbA1c values from baseline greater than sitagliptin. Exenatide XR, dulaglutide, and liraglutide also were associated with increased weight loss compared with sitagliptin. Treatment with liraglutide reduced HbA1c and resulted in greater weight loss than treatment with saxagliptin. However, there was low strength evidence that gastrointestinal adverse events were

lower with sitagliptin than with exenatide XR, liraglutide, albiglutide and dulaglutide. Gastrointestinal adverse events were also lower with saxagliptin than with liraglutide.

The 8 trials that compared a SGLT2 inhibitor with a DPP-inhibitor provided moderate-strength evidence that treatment with canagliflozin decreased HbA1c and increased weight loss from baseline compared with sitagliptin. Empagliflozin treatment was also associated with greater weight loss than with sitagliptin or linagliptin based on moderate-strength evidence. Additionally, there was moderate-strength evidence that empagliflozin treatment resulted in decreased HbA1c and increased proportions of patients achieving an HbA1c <7% compared with linagliptin. There was low strength evidence that dapagliflozin was associated with greater weight loss than saxagliptin and that sitagliptin treatment resulted in greater numbers of patients with <7% HbA1c at study's end than with canagliflozin 100 mg. However, treatment with sitagliptin resulted in lower rates of genital infections than treatment with canagliflozin and empagliflozin based on low-strength evidence. Rates of genital infections were also lower with saxagliptin compared with dapagliflozin and with linagliptin compared with empagliflozin.

Twelve studies compared a newer diabetes drug with metformin. There was moderate-strength of evidence that treatment with metformin improved HbA1c values more than linagliptin, alogliptin, and sitagliptin but less improvement was found with metformin than with dulaglutide (low-strength evidence). There was also low-strength evidence of greater weight loss with metformin than with sitagliptin, alogliptin, dulaglutide, and linagliptin, but metformin was associated with less weight loss when compared with canagliflozin, dapagliflozin, and empagliflozin. Treatment with metformin was also associated with greater gastrointestinal adverse events than was sitagliptin and alogliptin.

Four trials compared either a fixed-dose combination product or dual therapy with a DPP-4 inhibitor and metformin. There was low- to moderate-strength evidence that dual therapy with alogliptin, linagliptin, sitagliptin, canagliflozin, and empagliflozin in combination with metformin reduced HbA1c values more than component monotherapy. Weight loss in combination therapy with metformin was also improved compared with alogliptin or canagliflozin treatment alone. However, there was low-strength evidence that both the combination of alogliptin and metformin therapy and metformin therapy alone were associated with more frequent gastrointestinal adverse events versus alogliptin alone.

Conclusion

As a class, GLP-1 analogs reduce HbA1c and increase weight loss to a greater degree than DPP-4 inhibitors, but at the risk of increased gastrointestinal side effects. As a class, SGLT2 inhibitors also improve HbA1c and weight compared with DPP-4 inhibitors but at greater risk of genital infection. Treatment with metformin alone was associated with better HbA1c values and greater weight loss than several DPP-4 inhibitors but less weight loss than with several SGLT-2 inhibitors. However, while overall weight loss and weight loss differences between drugs and drug classes may be statistically significant, these differences may not clinically meaningful in some cases. Dual therapy or a fixed-dose combination product including metformin resulted in improved HbA1c values than component monotherapy.

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INTRODUCTION

Diabetes mellitus (diabetes) is a chronic disease associated with significant morbidity and healthcare costs. The prevalence of diabetes among adults has increased substantially over the past 2 decades, raising from 9.8% in the 1988 to 1994 period to 12.4% in the 2011 to 2012 period.[1] In 2010, approximately 21 million adults in the United States had diabetes, based on self-report or hemoglobin A1c (HbA1c) levels ≥6.5%.[2] Among people diagnosed with diabetes, 90% to 95% have type 2 diabetes, while 5% to 10% have type 1 diabetes.[3] Type 1 diabetes is characterized by autoimmune destruction of beta cells of the pancreas resulting in absolute insulin deficiency. Type 2 diabetes encompasses a heterogeneous group of disorders characterized by slow progressive loss of beta cell function and mass, leading to variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Higher glucagon levels relative to insulin also play a significant role in the pathogenesis and management of type 2 diabetes.

The 2016 American Diabetes Association treatment guidelines recommend an HbA1c goal of <7% for most nonpregnant adults in order to prevent adverse microvascular and macrovascular outcomes.[4] The guidelines acknowledge that less stringent (HbA1c <8%) or more stringent (HbA1c <6.5%) goals may be appropriate for certain populations.[5] Insulin is the standard treatment for type 1 diabetes. Pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin. Due to the progressive nature of diabetes, practitioners and patients often experience challenges in reaching and sustaining American Diabetes Association treatment goals. Patients with type 2 diabetes often need to take more than 1 type of diabetes medication. In 2005 and 2006, 35% of all patients with diabetes were taking 2 classes of antidiabetes medications, and 14% were taking 3 or more classes.[6]

Newer Diabetes Medications

Within recent years, several new antihyperglycemic agents have been approved (Table 1). These agents offer mechanisms of glycemic control beyond that of "traditional" oral agents and insulin by targeting alternate gluco-regulatory receptors and hormones such as amylin, GLP-1, glucose-dependent insulinotropic peptide (GIP), DPP-4, and sodium-glucose cotransporter 2 (SGLT2). For the purposes of this report, we consider the following to be "newer diabetes medications": amylin agonists, DPP-4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors. Amylin is a neuroendocrine hormone co-secreted with insulin from beta cells in response to elevated blood glucose concentrations, and it complements the actions of insulin. DPP-4 inhibitors block dipeptidyl peptidase 4 and reduce glucagon (and blood sugar levels) in the blood. GLP-1 and GIP are secreted by L- and K-type cells in the intestinal tract in response to a combination of endocrine and neural signals initiated by the entry of food into the gut. Secretion of GLP-1 and GIP enhance insulin release. Both endogenous GLP-1 and GIP are rapidly degraded by the proteolytic enzyme DPP-4. SGLT2 is located in the proximal renal tubules and is the main site of filtered glucose reabsorption from the tubular lumen. Inhibition of SGLT2 results in increased urinary excretion of glucose and reduced plasma glucose concentrations.

Dual Therapy and Fixed-dose Combination Products

For this report, we've included 10 fixed-dose combination products (FDCPs) approved for the treatment of type 2 diabetes. In addition, we've included studies of the individual components of those FDCPs when used together but in separate pills—we refer to this as "dual therapy" throughout the review. We only evaluate dual therapy when there is a US Food and Drug Administration-approved fixed dose combination product.

Table 1. Characteristics of included drugs

Class	Generic Name	Trade Name	Delivery
DPP-4 Inhibitors	Sitagliptin	Januvia®	Oral
	Saxagliptin	Onglyza®	Oral
	Linagliptin	Tradjenta®	Oral
	Alogliptin	Nesina®	Oral
GLP-1 Analogs (Incretin mimetics)	Albiglutide	Tanzeum™	Injection
	Dulaglutide	Trulicity®	Injection
	Exenatide	Byetta®	Injection
	Exenatide XR	Bydureon®	Injection
	Liraglutide	Victoza®, Saxenda®	Injection
Sodium-glucose co-transporter-2 inhibitor (SGLT2)	Canagliflozin	Invokana®	Oral
	Dapagliflozin	Farxiga®	Oral
	Empagliflozin	Jardiance®	Oral
Fixed Dose Combination Products (FDCPs)**	Alogliptin + Pioglitazone	Oseni	Oral
	Metformin + Sitagliptin	Janumet®	Oral
	Metformin + Sitagliptin XR	Janumet XR®	Oral
	Metformin ER + Saxagliptin	Kombiglyze XR®	Oral
	Metformin + Alogliptin	Kazano®	Oral
	Metformin + Linagliptin	Jentadueto®	Oral
	Metformin + Canagliflozin	Invokamet®	Oral
	Metformin + Empagliflozin	Synjardy®	Oral
	Metformin ER+ Dapagliflozin	Xigduo XR®	Oral
	Empagliflozin + Linagliptin	Glyxambi®	Oral

**The FDCPs or the individual components of those FDCPs used together but in separate pills (AKA dual therapy) are both included in the review

Scope and Key Questions

The purpose of this review is to assist healthcare providers, researchers, and policy makers in making clinical decisions, creating formularies, and developing policies regarding newer medications for the treatment of diabetes based on the most current available literature. We compare the efficacy and tolerability of newer diabetes medications and combinations, and also look for subgroups that may differ in these areas.

In the 2011 update report,[7] placebo-controlled comparisons were included as part of the evidence base. A new, streamlined approach was used for Update 1, which focuses on head-to-head studies. This streamlined approach was also carried forward for the current update. We compare efficacy and tolerability both within classes of newer diabetes medications and between the classes of newer diabetes medications; we also compare newer diabetes medications with metformin. For this update, we do not include comparisons of newer diabetes medications with pioglitazone or sulfonylureas. We also include trials enrolling populations of diabetes patients who are already on treatment with insulin or other oral medications for diabetes as long as they are randomized to an eligible drug and comparator.

We developed preliminary key questions to identify the populations, interventions, outcomes of interest, and eligibility criteria for studies. A draft of these questions and inclusion and exclusion criteria were posted on the Drug Effectiveness Review Project (DERP) website for public comment. The draft was reviewed and revised by representatives of the organizations participating in the DERP. These organizations approved the following key questions to guide the review for this report:

1. What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with type 2 diabetes mellitus?

2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with type 2 diabetes mellitus?

3. Are there subgroups of patients based on demographics (e.g. age, racial groups, gender), comorbidities (e.g., drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) differ in efficacy/effectiveness or tolerability and frequency of adverse events?

METHODS

Inclusion Criteria

Populations

- Adults with type 2 diabetes
- *Excluded: Children, individuals with Type 1 diabetes, individuals with gestational diabetes, pre-diabetes (impaired fasting glucose or impaired glucose tolerance), metabolic syndrome without diabetes, or polycystic ovary syndrome*

Interventions

"Newer diabetes medications" refer to DPP-4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors (see Table 1).

Comparators

- Other newer diabetes medications, fixed dose combination products containing a newer diabetes medication, metformin, or dual therapy with 1 or more newer diabetes medications
- Add-on therapy to any other diabetes medication

Efficacy and Effectiveness Outcomes

- Intermediate outcomes:
    1. Hemoglobin A1c (differences and proportions meeting targets)
    2. Changes in weight
- Health outcomes:

1. Microvascular disease: chronic kidney disease including renal dialysis, renal transplantation, end-stage renal disease and renal failure with proteinuria; retinopathy including proliferative retinopathy and blindness; peripheral neuropathy
2. Macrovascular disease: cardiovascular events, cardiovascular morbidity (e.g. myocardial infarction and peripheral arterial disease), cardiovascular mortality, stroke/TIA, coronary heart disease, cardiovascular procedures, extremity amputation
3. All-cause mortality

Harms/Adverse Events Outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events (e.g., diabetic ketoacidosis, non-ketotic hyperosmolar coma)
- Specific adverse events (e.g., cancers/neoplasms, infections, hypoglycemia, gastrointestinal effects, congestive heart failure, pancreatitis, weight gain, fractures)

Study Designs

- Good-quality systematic reviews
- Head-to-head randomized controlled trials for all outcomes (any size)
- For harms only, head-to-head prospective cohort and case-control studies (N≥100)

Duration

- For all study designs and all key questions ≥ 12 weeks

Literature Search

We searched Ovid MEDLINE® (1946 to February Week 1 2016), the Cochrane Database of Systematic Reviews® (2005 to February 3, 2016), and the Cochrane Central Register of Controlled Trials® (to January 2016) using included drugs, indications, and study designs as search terms (see Appendix C for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. We searched the US Food and Drug Administration's Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X7, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Titles and abstracts of citations identified through literature searches were first assessed for inclusion by 1 reviewer using the eligibility criteria above and a second reviewer checked all citations excluded by the first reviewer. Full-text articles of potentially relevant citations were retrieved and again were

assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published only in abstract form were not included because inadequate details were available for quality assessment.

Data Abstraction

We abstracted information on population characteristics, interventions, subject enrollment, and discontinuation and results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. We recorded intent-to-treat results when reported. If true intent-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intent-to-treat results. In cases where only per protocol results were reported, we calculated intent-to-treat results if the data for these calculations were available. Data abstraction was performed by 1 reviewer and independently checked by a second reviewer and differences were resolved by consensus.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria of the Drug Effectiveness Review Project.[8] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only possibly valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, 1 for effectiveness and another for adverse events.

The criteria used to rate observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality. We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

Two reviewers independently assessed the quality of each study and differences were resolved by consensus.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[9] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of newer diabetes medications and combinations. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

Strength of evidence is graded for each key outcome measure, and is limited to head-to-head comparisons except where a case can be made for assessing the strength of indirect evidence.

We graded the strength of evidence for the outcomes deemed to be of greatest importance to decision makers and those most commonly reported in the literature. For example, these included HbA1c and weight changes. Due to time and resource constraints, we did not grade the strength of evidence for every possible outcome reported in the included literature.

Table 2. Strength of evidence grades and definitions[9]

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies (published in a separate document).

We conducted meta-analyses of outcomes reported by at least 2 studies that were homogeneous enough to justify combining their results. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively. Random-effects models were used for meta-analysis of continuous outcomes (e.g., HbA1c and weight) measured

with the same scale, we report the weighted mean difference (WMD) between intervention and control subjects. For meta-analysis of binary outcomes, we report the relative risk (RR) and 95% confidence interval (CI). The Chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[10,11] An I^2 from 0 to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and ≥ 75% represents considerable heterogeneity.[12] The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for I^2). Whenever including a meta-analysis with considerable statistical heterogeneity in this report, we provide an explanation for doing so, considering the magnitude and direction of effects.[12] Potential sources of heterogeneity were examined by analysis of subgroups of study design, study quality, patient population, and variation in interventions. Quantitative analyses were conducted using Stata version 14.When meta-analysis could not be performed, the data were summarized qualitatively.

When describing conclusions and key findings in this report, we sometimes refer to "no difference" between 2 treatments. We use this wording to indicate that the available evidence did not support a statistically or clinically significant difference between the 2 treatments. For HbA1c outcomes, we note whether differences between groups were statistically significant. For weight outcomes, we did not set a cut-off at which we considered a change in weight to be clinically meaningful. We note the magnitude of effect and describe the SOE for the observed effect as discussed above.

Public Comment

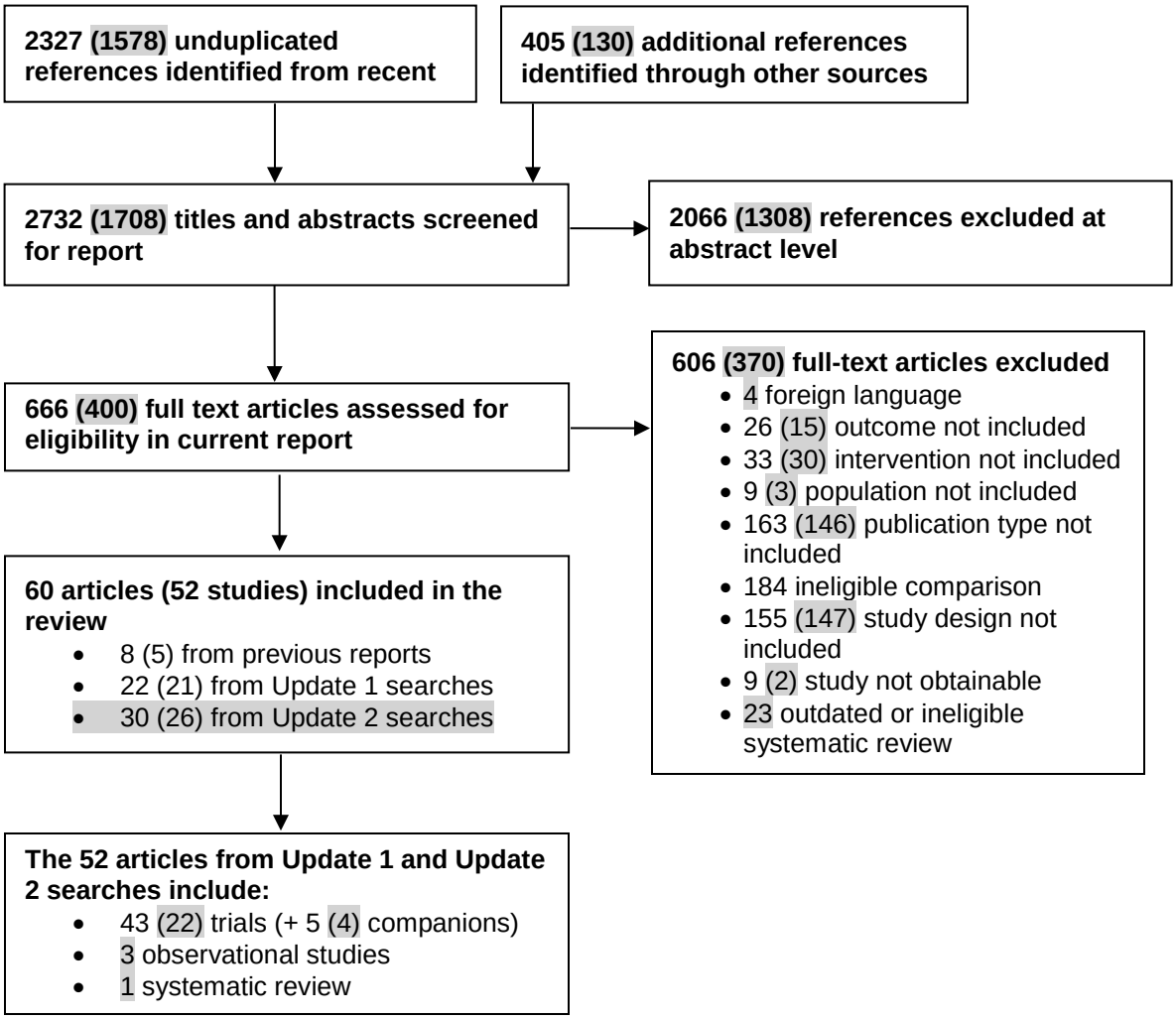
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 7 pharmaceutical companies as well as from the Academy of Managed Care Pharmacy.

RESULTS

Overview

A total of 2,732 citations (1,708 this update) were identified from comprehensive searches. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we identified 666 potentially includable citations (400 in this update). After reapplying the criteria for inclusion to the full texts of these citations, we ultimately included 52 studies in 60 publications: 5 studies (in 8 publications) from previous reports, 21 studies (in 22 publications) from Update 1 searches, and 26 studies[13-38] (in 30 publications)[13-42] from Update 2 searches. Of the 52 included studies, 43 were randomized controlled trials (22 in this update)[13,14,16-18,20-25,27-37] with 5 companion publications (4 in this update),[39-42] 3 were observational studies (all in this update),[15,19,26] and 1 was a systematic review (identified in this update).[38] We received dossiers from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Lilly, Merck, Novo Nordisk, and Takeda. Figure 1 shows the flow of study selection. Please see Appendix D for citations of studies excluded at full-text (Update 2 only).

Figure 1. Results of literature searches



[a] DERP uses a modified PRISMA flow diagram.[43]
[b] Shading indicate studies identified in Update 2. Unshaded study counts are cumulative.

Key Question 1. What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with type 2 diabetes mellitus?

I. Intra-class Comparisons (within a class)

Key Findings

- We found 10 fair-quality trials comparing 2 medications within the same class: 2 compared saxagliptin with sitagliptin and 8 compared 2 different GLP-1 analogs.
- We pooled data from 3 trials (n=1,225) comparing exenatide XR with exenatide administered twice daily over 24 to 30 weeks. Exenatide XR was more efficacious in reducing mean HbA1c than exenatide twice daily: weighed mean difference (WMD) −0.46%; 95% CI, −0.69 to −0.23 (strength of evidence: moderate).

- One trial (n=464) compared liraglutide 1.8 mg once daily with exenatide 10 µg twice daily over 26 weeks. Liraglutide was more efficacious than exenatide in reducing mean HbA1c: -0.33%; 95% CI, -0.47 to -0.18; *P*<0.0001 (strength of evidence: low).
- One trial (n=976) compared exenatide with dulaglutide and reported that rates of achieving HbA1c <7% were significantly higher for dulaglutide 1.5 mg (78%) and 0.75 mg (66%) than exenatide (52%) (All *P*<0.001). Similarly, mean change in HbA1c was also significantly greater in patients receiving dulaglutide than those receiving exenatide (*P*<0.001). Change in body weight was similar between exenatide and dulaglutide 1.5 mg (least-square mean difference: -0.24 kg; *P*=0.474), but change in body weight was significantly different in patients receiving dulaglutide 0.75 mg compared to exenatide (least-square mean difference: 1.27 kg; *P*<0.001) (strength of evidence: low).
- One trial (n=599) of dulaglutide compared with liraglutide found body weight was significantly reduced with liraglutide (treatment difference: 0.71 kg) (strength of evidence: low).
- One trial (n=841) of albiglutide compared with liraglutide found that mean HbA1c reduction and the proportion of patients achieving HbA1c <7% was significantly greater with liraglutide (RR 1.23, 95% CI 1.06 to 1.42) (strength of evidence: low). Liraglutide was also associated with significantly more weight loss (treatment difference: 1.55 kg, 95% CI 1.05 kg to 2.06 kg) (strength of evidence: low).

Overview

The prior report identified 6 trials comparing 2 drugs within the same class (1 trial compared saxagliptin with sitagliptin,[44] 1 compared liraglutide with exenatide XR,[45] and 3 trials compared exenatide XR (given once weekly) with exenatide given twice daily[46-48]. We rated 1 trial comparing liraglutide with exenatide XR as poor-quality, primarily due to inadequate handling of missing data[49]; other trials were rated fair-quality.

We identified 5 new trials comparing 2 drugs within the same class; 1 trial compared saxagliptin with sitagliptin,[24] 1 compared dulaglutide with liraglutide,[17] 1 compared dulaglutide with exenatide[37], 1 compared albiglutide with liraglutide[28], and 1 compared albiglutide with exenatide.[32] Sample sizes ranged from 66 to 835, and study durations ranged from 16 to 52 weeks. Patients in 3 studies were receiving background therapy with oral antidiabetes drugs,[24,28,37] while 2 studies enrolled patients who were drug naïve or only receiving metformin.[17,30] Mean ages ranged from 44 to 57 years and the proportion of females ranged from 40% to 74%. One Chinese trial enrolled only Asians; 1 trial predominately enrolled Whites (73% to 76%), with small proportions of American Indians (13% to 14%) and Blacks (7% to 9%); 1 trial reported ethnicity only as “not Hispanic or Latino” (75% to 76%); and ethnicity was not reported in 2 of the trials. All trials were fair-quality. Common methodologic shortcomings included inadequate description of allocation concealment and lack of blinding. Clinical health outcomes, including mortality and myocardial infarction, were rarely reported in the relatively short studies included here and were not designated as pre-specified outcomes in any study. Due to difficulty in interpreting these very infrequent events, we did not report clinical health outcomes unless they were experienced by ≥5% of the study sample.

We found no trials assessing intra-class comparisons of SGLT2 inhibitors.

Table 3. Characteristics of included studies: Newer diabetes medications within-class comparisons

Author, Year Trial Name	Arm Dose, mg/day (N)	Follow-up (weeks)	Back-ground Therapy	Quality
Included in the prior report				
Scheen, 2010[44]	SAXA 5 mg (403) SITA 100 mg (398)	18	Metformin	Fair
Blevins, 2011[46]	EXE 20 µg[a] (123) EXE XR 2 mg/w (129)	24	Metformin, sulfonylurea, TZD, or combination	Fair
Drucker, 2008[48]	EXE 20 µg[a] (147) EXE XR 2 mg/w (148)	30	Metformin, sulfonylurea, thiazolidinedione, or metformin plus either sulfonylurea or thiazolidinedione	Fair
Ji, 2013[47]	EXE XR 2 mg/w (340) EXE 20 µg[a] (338)	26	Metformin, sulfonylurea, TZD, or combination	Fair
New studies				
Li, 2014[24]	SAXA 5 mg (71) SITA 100 mg (68)	24	Metformin + another oral drug	Fair
Pratley, 2014[28] HARMONY 7	ALBI 30-50 mg (422) LIRA 0.6-1.8 mg (419)	32	Metformin and/or other oral drugs	Fair
Rosenstock, 2009[32]	EXE 5-10 µg (35) ALBI 30 (31)	16	Drug naïve or metformin only	Fair
Wysham, 2014[37] AWARD-1	DULA 1.5 (279) DULA 0.75 (280) EXE 5-10 µg (276)	26 (52 for harms)	Oral monotherapy or combination therapy	Fair
Dungan, 2014[17] AWARD-6	DULA 1.5 (299) LIRA 1.8 (300)	26	Metformin only	Fair

Abbreviations: ALBI, albiglutide; DULA, dulaglutide; EXE, exenatide; EXE XR, exenatide extended release; LIRA, liraglutide; mg, milligrams; N, number; SAXA, saxagliptin; SITA, sitagliptin; TZD, thiazolidinedione; µg, micrograms
[a] In these trials, patients were given exenatide 10 µg/day for 4 weeks followed by20 µg/day for the remainder of the trial period.

Detailed Assessment

DPP-4 Inhibitors

Overview

One fair-quality trial (n=801) included in the prior report compared sitagliptin 100 mg once daily with saxagliptin 5 mg once daily over 18 weeks,[44] and 1 new fair-quality trial (n=139) compared sitagliptin 100 mg once daily with saxagliptin 5 mg over 24 weeks (Table 3).[24]

Sitagliptin compared with saxagliptin

Saxagliptin and sitagliptin produced similar reductions in mean HbA1c over 18 (-0.52% vs. -0.62%) or 24 weeks (-1.34% vs. -1.07%),[24,44] and rates of achieving an HbA1c <7% did not significantly differ between groups (saxagliptin vs. sitagliptin, 33% vs. 39%; pooled RR 0.88, 95% CI 0.74 to 1.05; I^2=0%).

GLP-1 Analogs

Overview

Four fair-quality trials and 1 poor-quality trial from the prior report and four new fair-quality trials compared different GLP-1 analogs (Table 3). Three compared exenatide XR 2 mg once weekly with exenatide 10 µg twice daily; in all 3 trials, exenatide was initially given as 5 µg twice daily for 4 weeks, then increased to 10 µg twice daily.[46,47] One trial each compared liraglutide 1.8 mg once daily with exenatide 10 µg twice daily,[45] dulaglutide 0.75 mg or 1.5 mg once weekly with exenatide 5-10 µg twice daily,[37] dulaglutide 1.5 mg once weekly with liraglutide 1.8 mg once daily,[17] albiglutide 30 mg once weekly with exenatide 5 to 10 µg twice daily,[32] and albiglutide 30 to 50 mg once weekly with liraglutide 0.6 to 1.8 mg once daily.[28] Study duration ranged from 16 to 32 weeks, with most trials conducted for 26 weeks. All trials included adults with type 2 diabetes inadequately controlled on metformin, a sulfonylurea, a TZD, or combinations of these drugs. Mean ages ranged from 50 to 57 years, and 40% to 74% of participants were women.

Exenatide XR compared with exenatide

Three trials compared exenatide XR (administered once weekly) with twice daily formulation.[46,47] Our meta-analysis (3 trials, n=1,225) from the prior report found that exenatide XR 2 mg once weekly was more efficacious than exenatide 10 µg twice daily in reducing mean HbA1c over 24 to 30 weeks (WMD -0.46%; 95% CI -0.69 to -0.23).

Two trials found no statistically significant difference between the two drugs for changes in weight; both drugs were associated with weight loss.[46,48] The trial by Ji et al. found a greater reduction in weight with exenatide 10 µg twice daily than with exenatide XR (-2.45 kg, 95% CI -2.29 to -2.62 versus -1.63, 95% CI -1.47 to -1.79, respectively, $P<0.001$).[47]

Exenatide compared with liraglutide

One trial (n=464) compared liraglutide 1.8 mg once daily with exenatide 10 µg twice daily over 26 weeks; persons on a maximally tolerated doses of metformin, a sulfonylurea, or both were included.[45] No health outcomes were reported. Liraglutide was more efficacious than exenatide in reducing mean HbA1c (-1.12% [SE 0.08] compared with -0.79% [SE 0.08]; estimated treatment difference -0.33%; 95% CI -0.47 to -0.18; $P<0.0001$).[45] No difference was found in weight loss between the 2 groups (liraglutide -3.24 kg [0.33] compared with exenatide -2.87 kg [0.33]; estimated treatment difference -0.38 kg; 95% CI -0.99 to 0.23; $P=0.2235$).[45]

Exenatide compared with dulaglutide

One trial (n=976) compared exenatide 5 to 10 µg twice daily with dulaglutide 0.75 mg or 1.5 mg once weekly over 26 weeks in patients already on metformin and/or pioglitazone.[37] Rates of achieving HbA1c <7% were significantly higher for dulaglutide 1.5 mg (78%) and 0.75 mg (66%) than exenatide (52%) (All $P<0.001$). Similarly, mean change in HbA1c was also significantly greater in patients receiving dulaglutide than those receiving exenatide ($P<0.001$). Change in body weight was similar between exenatide and dulaglutide 1.5 mg (least-square mean difference: -0.24 kg; $P=0.474$), but body weight was significantly increased in patients receiving dulaglutide 0.75 mg compared to exenatide (least-square mean difference: 1.27 kg; $P<0.001$).

Exenatide compared with albiglutide

One trial (n=66) compared albiglutide 30 mg once weekly with exenatide 5 to 10 µg twice daily over 16 weeks in patients who were drug naïve or treated with metformin monotherapy only.[32] Mean change in HbA1c did not differ between groups (-0.87% vs. -0.54%). More subjects receiving albiglutide achieved an HbA1c <7% than those receiving exenatide, but the difference was not significant (52% vs. 35%; RR 1.47, 95% CI 0.82 to 2.60). No significant differences were reported for weight reduction.

Dulaglutide compared with liraglutide

One trial (n=599) compared dulaglutide 1.5 mg once weekly with liraglutide 1.8 mg once daily over 26 weeks in patients on a stable dose of metformin ≥1,500 mg per day.[17] Mean reduction in HbA1c (-1.42% vs. -1.36%) and the proportion of patients achieving HbA1c <7% (68% vs. 68%) did not differ between groups. Reduction in body weight was significantly greater in patients receiving liraglutide (-2.90 kg vs. -3.61 kg; mean difference, 0.71 kg; *P*=0.011).

Albiglutide compared with liraglutide

One trial (n=841) compared albiglutide 30 to 50 mg once weekly to liraglutide 0.6 to 1.8 mg once daily over 32 weeks in patients with diabetes uncontrolled by metformin, TZDs, sulfonylureas, or combination therapy.[28] Mean change in HbA1c was significantly greater in patients receiving liraglutide (-0.79% vs. -0.99%; treatment difference 0.21%, 95% CI 0.08% to 0.34%). Likewise, the proportion of patients achieving HbA1c <7% was greater for liraglutide compared to albiglutide (52% vs. 42%; RR 1.23, 95% CI 1.06 to 1.42). Weight loss was also significantly greater for liraglutide compared to albiglutide (-2.19 kg vs. -0.64 kg; treatment difference 1.55 kg, 95% CI 1.05 to 2.06 kg).

II. Between-Class Comparisons

Key Findings

- Sixteen trials compared a drug from 1 class of newer diabetes medications with a drug from a different class; 8 trials compared a DPP-4 inhibitor with a GLP-1 analog and 8 compared a DPP-4 inhibitor with an SGLT2 inhibitor. There were no trials that compared a GLP-1 analog with a SGLT2 inhibitor.
- No trial assessed health outcomes as a primary outcome; we found no evidence or insufficient evidence to determine the comparative efficacy for improving health outcomes for most between-class comparisons.

DPP-4 inhibitors compared with GLP-1 analogs

- Pooled data from 2 trials (n=753) found that exenatide XR was more efficacious than sitagliptin 100 mg once daily in reducing mean HbA1c over 12 to 26 weeks (WMD -0.48; 95% CI -0.69 to -0.26) and weight (WMD -1.32; 95% CI -1.87 to -0.76), and achieving a HbA1c < 7% (62% vs. 39%; RR 1.57, 95% CI 1.34 to 1.83, I^2=0), (low strength of evidence for all outcomes)
- One trial (n=665) found liraglutide 1.2 mg and 1.8 mg associated with improved HbA1c results (reduction over sitagliptin: -0.34% for 1.2 mg and -0.60% for 1.8 mg), greater proportion of participants who achieved a HbA1c < 7% (OR 2.75, 95% CI 1.78 to 4.25; OR 4.5, 95% CI 2.90 to 6.97); and greater weight loss (-2.86 to -3.38kg vs. -0.96kg) with

liraglutide versus sitagliptin at 26 weeks; results were similar at 52 weeks; a second study had similar findings (n=653) but only 80% of randomized patients were included in the analysis (low strength of evidence for all outcomes)

- One 104-week trial (n=628) found albiglutide 30 mg associated with greater improvement in HbA1c from baseline compared with sitagliptin (-0.63% vs. 0.28%) and greater weight loss (1.21 kg vs. 0.86 kg) but similar proportion of patients who achieved a HbA1c < 7% (39% vs. 32%; RR 1.22, 95% CI 0.98 to 1.52), (low strength of evidence for all outcomes)
- One adaptive trial that reported 26- , 52-, and 104- week outcomes provided low strength of evidence that treatment with dulaglutide 0.75 mg or 1.5 mg resulted in a greater likelihood of achieving a HbA1c < 7% compared with sitagliptin (55% and 61% vs. 38%, $P<0.001$) at 26 weeks, with similar results at 104 weeks (45% and 54% vs. 31%, $P<0.001$ for both comparisons) Both doses of dulaglutide were associated with greater reduction in body weight compared with sitagliptin at 26 weeks ($P<0.001$) but only the higher dose was so associated at 104 weeks ($P<0.05$).
- One trial (n=121) conducted in China provided low strength evidence that liraglutide 1.2 mg is associated with greater reductions in HbA1c and greater weight loss than treatment with saxagliptin 5 mg. There were no differences in proportions of patients who achieved an HbA1c < 7%.

DPP-4 inhibitors compared with SGLT2 inhibitors

- A good-quality systematic review of 3 studies (n=1575) found moderate strength evidence that canagliflozin 300 mg reduced HbA1c 0.24% more than sitagliptin 100 mg ($P=0.002$) and that canagliflozin 300 mg was associated with greater weight loss than sitagliptin by 2.84 kg ($P<0.001$). Results were mixed and provided low strength evidence of improved proportions achieving HbA1c < 7% with canagliflozin 300 mg versus sitagliptin.
  We found low strength evidence based on 1 trial (n=734) that canagliflozin 100 mg is associated with decreased likelihood of achieving HbA1c <7% than sitagliptin 100 mg (41% vs. 51%; OR 0.66, 95% CI 0.48 to 0.91).
- Two trials (n=883) provided moderate strength of evidence of improved weight loss with empagliflozin compared with sitagliptin but no difference between drugs in lowering HbA1c or in proportions who achieved a HbA1c < 7% with empagliflozin 25 mg and sitagliptin (44% vs. 38%; RR 1.17, 95% CI 0.96 to 1.43) or between empagliflozin 10 mg and sitagliptin (32% vs. 38%; RR 0.88, 95% CI 0.70 to 1.10).
- Two trials provided moderate strength of evidence that treatment with empagliflozin 25 mg improves the likelihood of achieving a HbA1c <7% more than treatment with linagliptin 5 mg (OR 3.3, 95% CI 1.9 to 4.6) as does treatment with empagliflozin 10 mg versus linagliptin (OR 3.3, 95% CI 1.9 to 4.7); overall HbA1c was reduced more with either dose of empagliflozin compared with linagliptin and patients also lost more weight with empagliflozin (mean weight loss 2 to 3 kg with empagliflozin vs. 0.7 to 0.8 kg with linagliptin).
- One trial provided low strength of evidence that treatment with dapagliflozin 10 mg increased weight loss when compared with saxagliptin 5 mg in patients poorly controlled on metformin (2.4 kg, 95% CI 2.9 kg to 1.9 kg vs. 0 kg, 95% CI −0.5 to 0.5) but there was no difference in proportions of patients who achieved an HbA1c < 7%.

Overview

Seven trials from the prior report and 12 additional trials (Table 4) and 1 systematic review identified new to this report compared a drug from 1 class of newer diabetes medications with a drug from a different class. Twelve trials[13,20-22,25,35,41,50-53] compared a DPP-4 inhibitor with a GLP-1 analog, Eight trials[16,23,29,31,33,54-56] and 1 systematic review[38] compared a DPP-4 inhibitor with an SGLT2 inhibitor. Study duration ranged from 12 to 104 weeks; no trials included health outcomes as a primary outcome of interest. Most trials excluded persons with significant comorbid conditions (including liver, kidney, and cardiovascular disease). One study in patients with diabetes and renal impairment [22] is discussed in Key Question 3. Two studies were rated poor quality[21,35] for unclear methods of randomization and allocation concealment, failure to report baseline characteristics of population randomized, lack of blinding, lack of intention to treat analysis, and lack of reporting of attrition and are not discussed further. Three studies were rated good-quality,[29,54,56] and the remainder were rated fair quality. A more detailed description of study characteristics and included populations by drug comparison is given below.

Table 4. Characteristics of included studies: Newer diabetes medications between-class comparisons

Author, Year Trial Name	Arm Dose, mg/day (N)	Follow-up (weeks)	Back-ground Therapy	Quality
Bergenstal, 2010[50]	EXE XR 2 mg/w (170) SITA 100 mg (172)	26	Metformin	Fair
Russell-Jones, 2012[51]	EXE XR 2.0 mg/w (248) MET 2,000 mg (246) SITA 100 mg (163)	26	None	Fair
Charbonnel, 2013[52]	SITA 100 mg (326) LIRA 0 1.2 mg-1.8 mg (327)	12	Metformin (some in the SITA group also received glimepiride at 12 weeks)	Fair
Pratley, 2010[53] Pratley, 2011[57]	LIRA 1.2 mg (225)a LIRA 1.8 mg (221) SITA 100 mg (219)	26,52	Metformin	Fair
Lavalle-Gonzalez, 2013[54]	SITA 100 mg (366) CANA 100 mg (368) CANA 300 mg (367)	52	Metformin	Good
Rosenstock, 2012[55],Nicolle, 2012[58]	SITA 100 mg (65) CANA 100 mg (64) CANA 300 mg (64)	12	Metformin	Fair
Schernthaner, 2013[56]	SITA 100 mg (378) CANA 300 mg (378)	52	Metformin + Sulfonylurea	Good
New studies				
Ahren, 2014[13] HARMONY 3	ALBI 30-50 mg (315) SITA 100 mg (313)	104	Metformin	Fair
Gudipaty, 2014[20]	EXE 20 µg (17)	24	None	Fair

Author, Year Trial Name	Arm Dose, mg/day (N)	Follow-up (weeks)	Back-ground Therapy	Quality
	SITA 100 mg (13)			
LI, 2014[25]	LIRA 1.2 mg (68) SAXA 5 mg (68)	24	Metformin± Sulfonylurea± TZDs± α-glucosidase inhibitors	Fair
Weinstock, 2015[41] AWARD-5	DULA 1.5 mg (304) DULA 0.75 (302) SITA 100 mg (315)	104	Metformin	Fair
Rosenstock, 2013[33]	EMPA 10 mg (71) EMPA 25 mg (70) SITA 100 mg (71)	12	Metformin	Fair
Roden, 2013[29]	EMPA 10 mg (224) EMPA 25 mg (224) SITA 100 mg (223)	24	None	Good
Lewin, 2015[23]	EMPA 25 mg/ LINA 5 mg (137) EMPA 10 mg/ LINA 5 mg (136) EMPA 25 mg (135) EMPA 10 mg (140) LINA 5 mg (132)	52	None	Fair
Rosenstock, 2015[31]	SAXA 5 mg/ DAPA 10 mg SAXA 5 mg DAPA 10 mg	24	Metformin XR	Fair
DeFronzo, 2015[16]	EMPA 10 mg/ LINA 5 mg EMPA 25 mg/ LINA 5 mg EMPA 10 mg LINA 5 mg	24,52	Metformin	Fair

Abbreviations: ALBI, albiglutide; CANA, canagliflozin; DULA, dulaglutide; EMPA, empagliflozin; EXE, exenatide; EXE XR, exenatide extended release; LINA, linagliptin; LIRA, liraglutide; MET, metformin; mg, milligrams; N, number; SAXA, saxagliptin; SITA, sitagliptin

[a] N in the extension study included 155 in the liraglutide 1.2 mg group, 176 in the liraglutide 1.8 mg group, and 166 in the sitagliptin 100 mg group

Detailed Assessment

DPP-4 inhibitors compared with GLP-1 analogs

Overview

Eight fair-quality trials compared a DPP-4 inhibitor with a GLP-1 analog.[13,20,25,27,50-53] All but 1 trial[25] compared a GLP-1 analog with sitagliptin 100 mg. Three trials compared sitagliptin with

exenatide,[20,50,51] 2 compared sitagliptin with liraglutide.[52,53] and 1 trial each compared sitagliptin with dulaglutide[41] and albiglutide.[13] One trial compared liraglutide with saxagliptin.[25] Mean ages for study populations ranged from 47 to 63 years and 34% to 52% of participants were women.

Sitagliptin compared with exenatide XR

Two trials (n=753) compared sitagliptin with exenatide XR over 26 weeks (Table 4).[50,51] Patients in both studies had a mean baseline HbA1c of 8.5%. In 1 study of patients with diabetes for 5.5 years participants continued their stable dose of metformin.[50] Patients were treatment-naïve and had diabetes for 2.7 years in the other study.[51] Our meta-analysis provided low strength evidence that exenatide XR was more efficacious than sitagliptin 100 mg once daily in reducing mean HbA1c over 26 weeks (WMD −0.48; 95% CI, −0.69 to −0.26). The proportion of patients who achieved reduction in HbA1c to <7% also favored exenatide XR (62% vs. 39%; RR 1.57, 95% CI 1.34 to 1.83, I^2=0). We also found that exenatide XR was associated with greater weight loss over 26 weeks compared with sitagliptin 100 mg once daily (WMD −1.32; 95% CI, −1.87 to −0.76).

Sitagliptin compared with exenatide

One trial (n=26) compared exenatide 10 µg with sitagliptin 100 mg in patients with impaired fasting glucose or type 2 diabetes (duration of diabetes 4.3 years) defined by a plasma glucose between 110 and 159 mg/dL after a wash-out period.[20] Patients' baseline HbA1c was 6.4%. There was no difference between 24-week HbA1c and baseline in either group or between sitagliptin and exenatide but sample sizes were extremely small and the strength of evidence considered insufficient from which to draw any meaningful conclusions.

Sitagliptin compared with liraglutide

Two trials compared liraglutide 1.2 mg, and/or 1.8 mg with sitagliptin 100 mg.[52,53] In both trials patients were inadequately controlled on metformin with mean baseline HbA1C between 8.2% and 8.5%[28,52] and mean duration of diabetes between 6 and 8 years. There was low strength evidence that HbA1c values were improved and weight was decreased with liraglutide compared with sitagliptin.

One trial (n=665) compared liraglutide 1.2 mg daily and liraglutide 1.8 mg daily with sitagliptin 100 mg daily over 26 weeks;[53] this trial also included a26-week extension period.[57] All study participants were on metformin ≥1500 mg daily as background therapy.

Liraglutide (at both dosages) was more efficacious in reducing mean HbA1c compared with sitagliptin over 26 weeks (change in HbA1c: liraglutide 1.2 mg −1.24%; liraglutide 1.8 mg −1.5%; sitagliptin −0.6%; P<0.0001 for both doses of liraglutide compared with sitagliptin). The differences in mean HbA1c at 26 weeks were −0.34% (95% CI −0.51 to −0.16) for liraglutide 1.2 mg once daily compared with sitagliptin 100 mg once daily and −0.60% (95% CI −0.77 to −0.43) for liraglutide 1.8 mg once daily compared with sitagliptin 100 mg once daily. Odds ratios for the proportion of participants who achieved HbA1c <7% for liraglutide 1.8 mg and liraglutide 1.2 mg versus sitagliptin were OR 4.5 (95% CI 2.90 to 6.97) and OR 2.75 (95% CI 1.78 to 4.25), respectively. Low strength evidence also indicated that liraglutide was associated with greater weight loss (at both dosages) compared with sitagliptin over 26 weeks (change in weight: liraglutide 1.2 mg, −2.86 kg; liraglutide 1.8 mg, −3.38 kg; sitagliptin, −0.96 kg; P<0.0001 for both comparisons).

Similarly, at 52 weeks (n=497 enrolled in the extension phase, 77% of 665 initially randomized) both dosages of liraglutide were more efficacious in reducing mean HbA1c compared with sitagliptin: liraglutide 1.2 mg daily, −1.29 % (95% CI −1.43 to −1.15); liraglutide 1.8 mg daily, −1.51% (95% CI −1.65 to −1.37); sitagliptin 100 mg daily, −0.88% (95% CI −1.02 to −0.74), *P*<0.0001 for both comparisons. The differences in mean HbA1c at 52 weeks were −0.40% (95% CI −0.59 to −0.22) for liraglutide 1.2 mg once daily compared with sitagliptin 100 mg once daily and −0.63% (95% CI −0.81 to −0.44) for liraglutide 1.8 mg once daily compared with sitagliptin. More patients achieved the composite outcome of HbA1c <7%, with no weight gain, and no confirmed major or minor hypoglycemia with liraglutide 1.8 mg and 1.2 mg compared with sitagliptin (OR 4.37, 95% CI 2.74 to 6.98; OR 2.80, 95% CI 1.74 to 4.48, respectively). At 52 weeks, liraglutide (at both doses) was associated with greater weight loss than sitagliptin 100 mg daily; between-group difference for liraglutide 1.2 mg compared with sitagliptin 100 mg daily was −1.62 kg (95% CI −2.43 to −0.82) and for liraglutide 1.8 mg compared with sitagliptin 100 mg daily, the difference was −2.53 kg (95% CI −3.33 to 1.72), *P*<0.001 for both comparisons.

The second trial enrolled 653 diabetes patients and compared liraglutide 1.2 mg with sitagliptin 100 mg for 26 weeks.[52] After 12 weeks individuals with HbA1c ≥7% and a fasting plasma glucose >110 mg/dL were either given glimepiride beginning at 1 mg/day if randomized to sitagliptin or were uptitrated to 1.8 mg of liraglutide if in the liraglutide group. The mean change from baseline to week 26 was −1.4% (95% CI −1.5 to −1.3) in those who received liraglutide and almost identical to the mean change among those taking sitagliptin −1.3% (95% CI −1.4 to −1.3). The proportion of patients with HbA1c <7% at week 26 was lower in the sitagliptin group (63% vs. 72%; difference in proportions −9.5% (95% CI −17.4 to −1.5). However, only 80% of patients randomized were analyzed in the per protocol analysis (522/653) due to missing HbA1c values or major protocol violations.

Sitagliptin compared with albiglutide

One trial (HARMONY 3, n=628) compared 104 weeks treatment with albiglutide 30 mg weekly with sitagliptin 100 mg daily in patients with type 2 diabetes taking metformin.[13] The mean duration of diabetes was 6 years and the mean baseline HbA1c was 8.1%. Patients experiencing persistent hyperglycemia and taking albiglutide could be uptitrated to 50 mg if predefined fasting plasma glucose or HbA1c values were met. At week 104 low strength evidence found albiglutide treatment to produce greater reduction in HbA1c from baseline compared with sitagliptin (−0.63% vs. -0.28%, *P*<0.001) but similar likelihood of achieving an HbA1c < 7% (39% vs. 32%; RR 1.22, 95% CI 0.98 to 1.52). At week 104 patients taking albiglutide lost a mean of 1.21 kg compared with 0.86 kg in those taking sitagliptin which was not significantly different (low strength of evidence for all outcomes).

Sitagliptin compared with dulaglutide

One trial (AWARD-5, n=230) in which patients in all groups received at least 1,500 mg of metformin throughout the study (other antidiabetic medications were discontinued) compared 26-weeks treatment with dulaglutide 0.75 mg, dulaglutide 1.5 mg, and sitagliptin 100 mg in patients with a mean duration of diabetes of 7 years and a mean baseline HbA1c of 8.1% and found both dulaglutide 0.75 mg and dulaglutide 1.5 mg associated with greater likelihood of achieving a HbA1c of <7% (55% and 61% vs. 38%, *P*<0.001 for comparisons with sitagliptin at

26 weeks).[27] Reductions in body weight were also greater with both doses of dulaglutide than with sitagliptin (*P*<0.001 for both comparisons).

This study followed an adaptive design and after the 26-week dose-finding phase of the study, patients who received 0.75 mg or 1.5 mg of dulaglutide or 100 mg of sitagliptin were retained in the study while participants randomized to other doses of dulaglutide were discontinued from the study.[41] A second randomization enrolled additional patients to the three remaining arms. Patients who initially were randomized to the placebo arm, received sitagliptin after 26 weeks. At 104 weeks (n=1,098; some patients treated for 104 weeks, some for 78 weeks) low strength evidence indicated that taking dulaglutide 0.75 mg (45%) or dulaglutide 1.5 mg (45%) resulted in increased likelihood of achieving a HbA1c <7% than taking sitagliptin (31%), RR 1.44 (95% CI 1.17 to 1.77) and RR 1.75 (95% CI 1.44 to 2.12), respectively. Weight loss was also greater for patients taking dulaglutide 1.5 mg (but not dulaglutide 0.75 mg) than with sitagliptin at 104 weeks (*P*<0.05), based on low strength evidence.

Saxagliptin compared with liraglutide

One trial (n=121) conducted in China compared liraglutide 1.2 mg to saxagliptin 5 mg in diabetes patients poorly controlled on monotherapy with either metformin or a sulfonylurea or dual or triple drug therapy.[25] The mean duration of diabetes was 5 years and the average baseline HbA1c of 8.5%. The mean change from baseline in HbA1c was greater in those given liraglutide (−1.50%, 95% CI −1.67 to −1.34) compared with saxagliptin (−1.23%, 95% CI −1.36 to −1.11), *P*<0.01. There was no difference in the proportion of participants who achieved an HbA1c <7% at 24 weeks (51% vs 39%; RR 1.45, 95% CI 0.95 to 2.22). Compared with baseline values, patients in the liraglutide group lost more weight than those receiving saxagliptin (−6.0 kg, 95% CI −6.8 to −5.3; −0.9 kg, 95% CI −1.5 to −0.4), respectively (low strength of evidence for all outcomes).

DPP-4 inhibitors compared with SGLT2 inhibitors

Overview

Eight trials compared a DPP-4 inhibitor with a SGLT2 inhibitor. Three trials[54-56] and 1 systematic review[38] compared canagliflozin with sitagliptin. Two trials compared empagliflozin with sitagliptin;[29,33] 2 trials compared empagliflozin with linagliptin;[16,23] and 1 trial compared dapagliflozin with saxagliptin.[31] Mean ages ranged from 52 to 59 years and 37% to 55% of participants were women. Three trials[29,54,56] and 1 systematic review[38] were rated good quality and the remaining trials were rated as fair.

Sitagliptin compared with canagliflozin

The results from a good-quality systematic review[38] that include all 3 trials of the comparison of canagliflozin with sitigliptin[54-56] are reported here. The mean baseline HbA1c ranged between 7.7% and 8.1%; the mean duration of diabetes ranged from 5.6 to 9.7 years. All patients received background metformin therapy and patients in 1 study also received a sulfonylurea.[56] Study lengths were 12 weeks,[55] 26 weeks with a 26 week extension,[54] and 52 weeks.[56] The systematic review provided moderate strength of evidence that both HbA1c values and weight are greater reduced with canagliflozin than with sitagliptin. In the pooled analysis (n=1575 for HbA1c and n=1593 for weight) that compared canagliflozin 300 mg with sitagliptin 100 mg, the difference of the mean change from baseline in HbA1c was −0.24% (95% CI −0.40 to −0.09) and in weight was −2.84 kg (95% CI −3.21 to −2.48).[38] We conducted a separate pooled analysis of 2 studies

that compared canagliflozin 300 mg with sitagliptin at 52 weeks and found a 20% increased probability of achieving HbA1c <7% with canagliflozin (51% vs. 43%; RR 1.20, 95% CI 1.07 to 1.33, I^2=74%).[54,56] However, statistical heterogeneity was significant. Although age, baseline BMI, and body weight were similar between the 2 studies, there was no difference between treatment with canagliflozin 300 mg and sitagliptin 100 mg in the study where patients had slightly lower baseline HbA1c (7.9% vs. 8.1%), shorter duration of diabetes (7 years vs. >9 years) and were not also given a background sulfonylurea along with metformin (55% vs. 51%; OR 1.28, 95% 0.92 to 1.76).[54] Additionally, this same study found canagliflozin 100 mg associated with a reduced likelihood of achieving a HbA1c <7% after 52 weeks compared with sitagliptin (41% vs. 51%; OR 0.66, 95% CI 0.48 to 0.91). Due to the conflicting evidence for likelihood of achieving an HbA1c < 7%, we rated this as low strength evidence for this outcome.

Sitagliptin compared with empagliflozin

Two studies compared empagliflozin 10 mg, empagliflozin 25 mg, and sitagliptin 100 mg.[29,33] Study duration was 12 weeks[33] with a 78-week extension to week 90[40] or 24 weeks.[29] One trial enrolled patients with duration of diabetes for less than 5 years who were treatment-naïve for the preceding 12 weeks,[29] while the other study enrolled patients on metformin therapy; most had diabetes for greater than 5 years.[33,40] Baseline HbA1c were similar in the 2 studies (7.9 to 8.1%). In the 12-week study (n=212), empagliflozin was given in a double-blind fashion, whereas sitagliptin was provided open-label. There were no differences in proportions of patients achieving a HbA1c <7% (38% with empagliflozin 10 mg vs. 37% with empagliflozin 25 mg vs. 34% with sitagliptin).[33] This trial was extended an additional 78 weeks and patients taking placebo or empagliflozin doses not selected to go forward were rerandomized to empagliflozin 10 mg or 25 mg and included with individuals from the initial randomization. Adjusted mean changes in HbA1c (adjusted for number of previously used antidiabetes medications, baseline HbA1c, fasting plasma glucose, blood pressure and country) were not different at 90 weeks between sitagliptin (−0.40%; 95% CI −0.60 to −0.20) and either dose of empagliflozin, There were no differences between empagliflozin 25 mg and sitagliptin (45% vs. 37%; RR 1.19, 95% CI 0.81 to 1.74) or between empagliflozin 10 mg and sitagliptin (27% vs. 37%; RR 0.72, 95% CI 0.48 to 1.10) in achieving <7%. At 90 weeks, both empagliflozin doses resulted in greater weight loss than sitagliptin (−0.4 kg, 95% CI −0.15 to 0.7) but were not different from each other (empagliflozin 25 mg: −4.30 kg, 95% CI −4.8 to −3.3; empagliflozin 10 mg: −3.1 kg, 95% CI −3.9 to −2.4).

In the second trial (n=671),[29] rated good-quality, patients were treatment naïve and had been diagnosed with diabetes for a shorter period of time than the previous study. There was no differences between the same 3 treatments in mean change from baseline in HbA1c at 24 weeks (empagliflozin 10 mg and sitagliptin: −0.66%, 95% CI −0.76 to −0.56; empagliflozin 25 mg: −78%, 95% CI −0.88 to −0.67). There was also little difference in proportion of patients achieving an HbA1c <7% between empagliflozin 25 mg and sitagliptin (44% vs. 38%; RR 1.16, 95% CI 0.92 to 1.47) and between empagliflozin 10 mg and sitagliptin (35% vs 38%; RR 0.94, 95% CI 0.73 to 1.22) and no difference between empagliflozin doses (RR 0.81, 95% CI 0.64 to 1.03). Patients in both empagliflozin groups lost a similar amount of body weight (2.26 kg with empagliflozin 10 mg and 2.48 kg with empagliflozin 25 mg) compared with a weight gain with sitagliptin of 0.18 kg (P<0.001 for both comparisons). Pooled analysis from the 2 trials indicated no difference between treatment with empagliflozin 25 mg and sitagliptin in proportions who achieved HbA1c <7% (44% vs. 38%; RR 1.17, 95% CI 0.96 to 1.43, I^2=0%) or between

empagliflozin 10 mg and sitagliptin (32% vs. 38%; RR 0.88, 95% CI 0.70 to 1.10, I^2=7%). These trials provided moderate strength of evidence of no difference between treatment with empagliflozin and sitagliptin in lowering HbA1c and moderate strength evidence of improved weight loss with empagliflozin compared with sitagliptin.

Linagliptin compared with empagliflozin

Two 24-week, fair-quality trials compared linagliptin with empagliflozin in patients who were either not receiving antidiabetic medication (n=370)[23] or were inadequately controlled on metformin (n=397).[16] The same team of authors conducted both studies and enrolled patients with a baseline HbA1c of approximately 8% although time since diagnosis of diabetes was shorter in the trial enrolling treatment-naïve patients where over a third of patients had the diabetes diagnosis for 1 year[23] or less compared with between 1 and 10 years for most participants in the other study.[16] In treatment-naïve patients the mean change in HbA1c from baseline was greater in patients treated with empagliflozin 25 mg or 10 mg compared with linagliptin 5 mg (difference of the mean change: −0.41%, 95% CI −0.61 to −0.22; −0.57%, 95% CI −0.76 to −0.37, respectively).[23] Patients receiving empagliflozin 25 mg or 10 mg were also more likely to achieve a HbA1c < 7% at 24 weeks compared with linagliptin (55% vs. 32%; OR 3.1 95% CI 1.8 to 5.3; 62% vs. 32%; OR 4.3, 95% CI 2.5 to 7.5, respectively).[23] Patients in both empagliflozin groups lost more body weight than the group receiving linagliptin (2 kg with empagliflozin 25 mg; 2.7 kg with 10 mg vs. 0.8 kg with linagliptin, *P*<0.01 for both comparisons).

Similarly, in the trial enrolling patients inadequately controlled on metformin, there were greater reductions in mean change in HbA1c from baseline in patients receiving add-on therapy with empagliflozin 25 mg (difference of the mean change: −0.50%, 95% CI −0.67 to −0.32) and empagliflozin 10 mg (difference of the mean change: −0.39%, 95% CI −0.56 to −0.21) compared with linagliptin.[16] Likewise, 62% of patients treated with empagliflozin 25 mg and 58% of patients treated with empagliflozin 10 mg versus 36% of patients given linagliptin achieved HbA1c <7% (OR 3.5, 95% CI 1.9 to 6.4; OR 2.8, 95% CI 1.6 to 5.0). Weight loss was also similar to the previous study. Patients lost on average 3 kg with empagliflozin 25 mg, 2.6 kg with empagliflozin 10 mg and 0.7 kg with linagliptin (*P*<0.001 for comparisons with linagliptin).

Pooled odds ratios provided moderate strength evidence of three times the likelihood of achieving a HbA1c <7% with empagliflozin 25 mg and empagliflozin 10 mg compared with linagliptin (OR 3.3, 95% CI 1.9 to 4.6, I^2=0%; OR 3.3, 95% CI 1.9 to 4.7, I^2=0%). Evidence was also moderate strength for greater overall reduction in HbA1c and increased weight loss with empagliflozin compared with linagliptin.

Saxagliptin compared with dapagliflozin

One fair-quality trial (n=355) enrolled patients who were poorly controlled on metformin to add-on therapy with saxagliptin 5 mg or dapagliflozin 10 mg.[31] Mean baseline HbA1c was approximately 9% and the mean duration of diabetes was between 7 and 8 years. The proportion of patients who achieved HbA1c <7% at 24 weeks were similar (23% with dapagliflozin vs. 17% with saxagliptin). Patients treated with dapagliflozin lost an average of 2.4 kg (95% CI 2.9 to 1.9) whereas with saxagliptin the mean weight change was 0 kg (95% CI −0.5 to 0.5).

III. Newer Diabetes Medications compared with Metformin

Key Findings

- Twelve trials compared a newer diabetes drug with metformin. Eight compared a DPP-4 inhibitor with metformin: linagliptin (1 trial), alogliptin (1 trial), sitagliptin (4 trials), and saxagliptin (2 trials). No trial assessed health outcomes as a primary outcome; we found insufficient evidence to determine the comparative efficacy for improving health outcomes for most between class comparisons.

DPP-4 inhibitors compared with metformin

- One trial (n=433) found no difference between linagliptin 5 mg and metformin 500 mg twice daily for reduction in HbA1c (low strength of evidence). Metformin 1,000 mg twice daily was more efficacious than linagliptin in reducing mean HbA1c (strength of evidence: moderate), between-group difference: −0.60% (95% CI −0.32% to −0.88%).
- One trial (n=433) found greater weight reduction with metformin (at 500 mg and 1,000 mg twice daily) compared with linagliptin at 24 weeks in 1 trial (strength of evidence: low). The difference in mean change from baseline for metformin 500 mg twice daily compared with linagliptin 5 mg once daily was −0.90 kg (95% CI −0.31 to −1.49); and −0.70 kg (95% CI −0.11 to −1.29) for linagliptin compared with metformin 1,000 mg twice daily.
- One trial found no difference between alogliptin 12.5 mg twice daily and metformin 500 mg twice daily at 26 weeks for reducing mean HbA1c (n=227), between-group difference: 0.09% (95% CI −0.17 to 0.35) (low strength of evidence). However, metformin 1,000 mg twice daily was more efficacious compared with alogliptin 12.5 mg twice daily (strength of evidence: moderate): between-group difference, −0.55% (95% CI −0.29 to −0.81, n=224).
- One trial found greater weight reduction with metformin (at both doses) compared with alogliptin 12 mg twice daily (n=338, strength of evidence: low). The difference in mean weight change from baseline for metformin 500 mg twice daily compared with alogliptin 12.5 mg twice daily was −0.79 kg (95% CI −0.003 to −1.58), and for metformin 1,000 mg twice daily compared with alogliptin 12.5 mg twice daily, the difference in mean weight change from baseline was −1.4 kg (95% CI −2.02 to −0.45).
- Metformin 2,000 mg daily was more efficacious than sitagliptin 100 mg daily in reducing mean HbA1c (strength of evidence: moderate). Our meta-analysis (3 trials; n=1655) found that metformin 2,000 mg per day was more efficacious than sitagliptin 100 mg daily (WMD −0.30%, 95% CI −0.52 to −0.09, I^2=84.7%); all trials found a statistically significant benefit favoring metformin, 1 trial found a smaller magnitude of effect (−0.14%) than the other 2 trials (−0.33% and −0.47%).
- Metformin 2,000 mg was associated with a greater reduction in weight compared with sitagliptin 100 mg over 24 to 54 weeks (strength of evidence: low); mean difference between groups ranged from −1.2 kg to −1.7 kg.
- Our meta-analysis (2 trials; n=1677) found no difference in HbA1c with the addition of saxagliptin 5 mg compared with uptitration of metformin in patients not at goal on submaximal doses of metformin (WMD −0.31, 95% CI −0.74 to 0.13) (strength of evidence: low). Two trials found inconsistent results; 1 trial found greater reduction in HbA1c with the addition of saxagliptin 5 mg compared with uptitration of metformin

(between-group difference: −0.53, 95% CI −0.74 to −0.32) and another trial found no difference in the change from baseline (between-group difference: −0.09%, 95% CI −0.26 to 0.08).

- In 1 trial (n=282), the uptitration of metformin was associated with a greater reduction in weight compared with adding saxagliptin 5 mg, between-group difference: −0.9 kg (95% CI −0.24 to −1.56).

GLP-1 analogs compared with metformin

- One trial (n=807) of dulaglutide compared with metformin found greater mean reduction in HbA1c and proportion of patients achieving HbA1c <7% with dulaglutide than metformin (RR 1.16, 95% CI 1.01 to 1.34) (strength of evidence: low). Weight change was less with dulaglutide 0.75 mg than metformin, while there was no difference in weight change between dulaglutide 1.5 mg and metformin (strength of evidence: low).

SGLT2 inhibitors compared with metformin

- We found no difference between dapagliflozin and metformin for reducing HbA1c. We pooled 2 trials (n=505) in a meta-analysis. There was no difference between dapagliflozin 5 mg compared with metformin XR 1,500 mg to 2,000 mg daily (WMD −0.12, 95% CI −0.16 to −0.08). Our meta-analysis of 2 trials (n=522) found that dapagliflozin 10 mg was associated with a small but statistically significant greater reduction in HbA1c compared with metformin XR 1,500 mg to 2,000 mg daily found (WMD −0.11%, 95% CI −0.11 to −0.05). The direction of effect favored dapagliflozin, but overall magnitude of effect was small and not within a range that is considered clinically significant.
- Dapagliflozin is associated with greater weight reduction over 24 weeks compared with metformin (strength of evidence: low). Our meta-analysis (2 trials; n=505) found a greater reduction with dapagliflozin 5 mg compared with metformin XR 1,500 mg to 2,000 mg daily (WMD −1.18 kg, 95% CI −1.86 to −0.26); similarly, a greater reduction in weight was seen with dapagliflozin 10 mg compared with metformin XR 1,500 mg to 2,000 mg (WMD −1.3 kg, 95% CI −1.8 to −0.7).
- Two trials (n=660 and 336) of empagliflozin compared with metformin found no differences in mean reduction in HbA1c or the proportion of patients achieving HbA1c <7% (strength of evidence: low). Weight was reduced more with empagliflozin over 52 weeks; while no difference in weight reduction was observed in the shorter (12-week) study for the lower dose of empagliflozin, both doses were associated with greater weight reduction in the extension of this trial (strength of evidence: low).
- One trial (n=1,186) of canagliflozin compared with metformin found no differences in mean HbA1c reduction or in the proportion of patients achieving HbA1c <7% (strength of evidence: low). Weight reduction was greater with canagliflozin 100 mg (−3.0 kg; treatment difference −0.9 kg, 95% CI −1.6 to −0.2 kg) and 300 mg (−3.9 kg; treatment difference −1.8 kg, 95% CI −2.6 to −1.1 kg) compared to metformin (−2.1 kg) (strength of evidence: low).

Twelve trials from the prior report and 3 newly identified trials compared a newer diabetes drug with metformin. Of these, 8 trials compared a DPP-4 inhibitor with metformin: linagliptin (1 trial)[59], alogliptin (1 trial),[60] sitagliptin (4 trials),[51,61-63] and saxagliptin (2 trials).[64,65] Of the trials comparing saxagliptin to metformin, 1 used extended-release formulation,[64] while

the other used an immediate-release formulation.[65] Three trials compared metformin with a GLP-1 analog; 1 trial compared with exenatide administered twice daily over 26 weeks,[66] 1 trial that compared with exenatide XR and sitagliptin,[51] and 1 trial compared with dulaglutide.[36] Six trials compared an SGLT2 inhibitor with metformin; 3 (in 2 publications) assessed dapagliflozin[67,68], 2 assessed empagliflozin[14,40] and 1 assessed canagliflozin[30]; this last trial also assessed the combination of canagliflozin and metformin. Table 5 presents study characteristics for included trials comparing newer diabetes drugs with metformin.

Table 5. Characteristics of included studies: Newer diabetes medications compared with metformin

Author, Year Trial Name	Arm Dose, mg/day (N)	Follow-up (weeks)	Back-ground Therapy	Quality
Included in the prior report				
Haak, 2012[59]	LINA 5 mg (142) MET 1,000 mg (144) MET 2000 mg (147) LINA 5 mg +MET 1,000 mg (143) LINA 5 mg + MET 2000 mg (143)	24	None	Fair
Haag, 2008[69]	LINA 5 mg (55) MET 1,000 mg – 2000 mg (65)	12	None	Fair
Pratley, 2014[60]	ALO 25 mg[a] (112) ALO 25 mg[b] (113) MET 1,000 mg (114) MET 2000 mg (111) ALO 25 mg + MET 1,000 mg (111) ALO 25 mg + MET 2000 mg (114)	26	None	Fair
Aschner, 2010[61]	SITA 100 mg 455) MET 2000 mg (439)[c]	24	None	Fair
Derosa, 2010 [62]	SIT 100 mg (75) MET 1700 mg (76)	52	PIO[d]	Fair
Goldstein, 2007[63] Williams-Herman, 2009[70] Williams-Herman, 2010[71]	SITA 100 mg (179) MET 1,000 mg (82) MET 2000 mg (182) SITA 100 mg+ MET 1,000 mg (190) SITA 100 mg+ MET 1,000 mg (182)	24, 54, 104	None	Fair
Russell-Jones, 2012[51]	EXE 2.0 mg/w MET 2,000 mg SITA 100 mg	26	None	Fair

Author, Year Trial Name	Arm Dose, mg/day (N)	Follow-up (weeks)	Back-ground Therapy	Quality
Fonseca, 2012[64]	SAXA 5 mg + MET XR 1500 mg (138) MET XR uptitrated to 2000 mg[e] (144)	18	MET XR 1500 mg	Fair
Hermans, 2012[65]	SAXA 5 mg (147) MET uptitrated to 2000 mg[f] (139)	24	MET 1500 mg	Fair
Yuan, 2012[66]	EXE 10 µg (33) MET1500 mg (25)[g]	26	None	Fair
Henry, 2012[68h]	DAPA 5 mg (203) MET XR 2000 mg (201)[i] DAPA 5 mg+ MET XR 2000 mg (194)	24	None	Fair
Henry, 2012[h68]	DAPA 10 mg (219) MET XR 2000 mg (208)[i] DAPA 10 mg+ MET XR 2000 mg (211)	24	None	Fair
List, 2009[67]	DAPA 5 mg (58) DAPA 10 mg (47) MET XR 1500 mg (56)[j]	12	None	Fair
New studies				
Araki, 2015[14]	EMPA 10 mg (136) EMPA 25 mg (137) MET 500-2,250 (63)	52	Sulfonylureas	Fair
Ferrannini, 2013[18,40]	EMPA 10 mg (106) EMPA 25 mg (109) MET (56)	12 + 90	None or metformin	Fair
Rosenstock, 2016[30]	CANA 100 mg + MET (237) CANA 300 mg + MET (237) CANA 100 mg (237) CANA 300 mg (238) MET (237)	26	None	Fair
Umpierrez, 2014[36]	DULA 1.5 mg (269) DULA 0.75 mg (270) MET 1,500-2,000 mg (268)	52 (primary analysis at 26)	None or monotherapy	Good

Abbreviations: ALO, alogliptin; CANA, canagliflozin; DAPA, dapagliflozin; DULA, dulaglutide; EMPA, empagliflozin; EXE, exenatide; LINA, linagliptin; MET, metformin; MET XR, metformin extended release; mg, milligrams; N, number; PIO, pioglitazone; SAXA, saxagliptin; SITA, sitagliptin; µg, micrograms

[a] Patients in this group were randomized to alogliptin 12.5 mg twice daily.

[b] Patients in this group were randomized to alogliptin 25 mg once daily.

[c] Eligible patients were started on metformin 500mg once daily and up-titrated to metformin 1,000mg twice daily during the initial 5 weeks of the study.
[d] This trial enrolled patients not at goal on pioglitazone 30mg/day. The group randomized to sitagliptin continued pioglitazone 30mg/d and the group randomized to metformin received pioglitazone 15mg/day. The reason for the discrepancy in pioglitazone doses was not explained.
[e] Eligible patients were stabilized on metformin XR 1500 mg daily during a lead-in period; those who had a HbA1c between 7.0 and 10.5 were randomized to receive to either the addition of saxagliptin 5 mg or uptitration of metformin XR to 2000 mg daily.
[f] Eligible patients were stabilized on metformin 1500 mg daily during a lead-in period; those who had a HbA1c between 7.0 and 10.5 were randomized to receive either the addition of saxagliptin 5 mg or uptitration of metformin to 2000 mg daily.
[g] Metformin was started at a dose of 500 mg twice daily for 4 weeks, then increased to 500 mg 3 times a day during weeks 4-12.
[h] The publication by Henry et. al. reports results from two separate trials, each with three arms. In one trial dapagliflozin was dosed at 5mg and in the other trial dapagliflozin was dosed at 10mg.
[i] Starting dose of metformin XR was 500 mg daily and increased to 2000mg daily over the initial 8 weeks of the study period.
[j] Starting dose of metformin XR was 750 mg daily and increased to1500mg at week 2.

All trials enrolled adults with type 2 diabetes. Study duration ranged from 12 to 26 weeks in most trials; 2 trials only reported outcomes at 52 weeks, and 1 trial included an extension period that reported outcomes at 54 and 102 weeks. Most excluded those with significant comorbid conditions or those who had an HbA1c >11.0. A more detailed description of study characteristics and included populations is given below by drug comparison.

Detailed Assessment

DPP-4 inhibitors compared with metformin

Overview

Eight trials compared a DPP-4 inhibitor with metformin: linagliptin (1 trial)[59], alogliptin (1 trial),[60] sitagliptin (4 trials),[51,61-63] and saxagliptin (2 trials).[64,65] One trial compared sitagliptin 100 mg daily to metformin 850 mg twice daily as add-on therapy in a population not controlled with pioglitazone monotherapy;[62] 2 trials compared the addition of sitagliptin to uptitration of metformin in patients who were not controlled on a submaximal dose of metformin.[64,65] The other 5 trials included people who were not taking any other medication for diabetes. Mean ages ranged from 52 to 59 years. In 3 trials, less than half of participants were women.[51,59,65] Across all other trials, women made up approximately half of the included population. All trials were rated as fair-quality.

Linagliptin compared with metformin

At 24 weeks, there was no significant difference in mean change from baseline HbA1c between those receiving linagliptin 5 mg daily and those receiving metformin 500 mg twice daily (−0.10%, 95% CI 0.18 to −0.30). Metformin 1,000 mg twice daily was more efficacious in reducing mean HbA1c than linagliptin 5 mg daily (−0.60%, 95% CI −0.88 to −0.32). Greater weight loss was seen with metformin (at both doses) compared with linagliptin at 24 weeks. The difference in mean change from baseline for metformin 500 mg twice daily and linagliptin 5 mg once daily was −0.90 kg (95% CI −1.49 to −0.31) and −0.70 kg (95% CI −0.29 to −1.11) for linagliptin compared with metformin 1,000 mg twice daily.[59]

Alogliptin compared with metformin

One trial compared alogliptin 25 mg daily (2 arms: 1 received 12.5 mg twice daily and the other received 25 mg once daily) with 2 doses of metformin (500 mg twice daily and 1,000 mg twice daily) over 26 weeks.[60] Alogliptin produced similar reductions in mean HbA1c regardless of schedule (alogliptin 25 mg once daily: −0.52% [no variance reported] and alogliptin 12.5 mg

twice daily: −0.56% [SE 0.093]). The trial did not compare alogliptin directly to metformin (only to a fixed drug combination, discussed in a separate section). We calculated the between-group difference for alogliptin 12.5 mg compared with metformin 500 mg at 26 weeks; there was no difference between groups (0.09%, 95% CI −0.17 to 0.35). Metformin 1,000 mg twice daily was more efficacious than alogliptin 12.5 mg twice daily in reducing mean HbA1c (between-group difference: −0.55%, 95% CI −0.29 to −0.81). For weight outcomes, metformin (at both dosages) was associated with greater weight loss than alogliptin 12.5 mg twice daily (−0.79 kg, 95% CI −0.003 to 1.58) for metformin 500 mg twice daily compared with alogliptin 12.5 mg twice daily (−1.4 kg, 95% CI −0.46 to 2.02) and for metformin 1,000 mg twice daily compared with alogliptin 12.5 mg once daily.

Sitagliptin compared with metformin

Four trials compared sitagliptin with metformin.[51,61-63] Three trials reported mean change from baseline HbA1c over 24 to 26 weeks.[51,61,63] One of these also reported outcomes from an extension trial over 54 and 102 weeks.[63,70,71] The fourth trial reported outcomes at 52 weeks only.[62] Our meta-analysis (3 trials; n=1655) found that metformin 2,000 mg per day was more efficacious than sitagliptin 100 mg daily (WMD −0.30%, 95% CI −0.52 to −0.09, I^2=85%). All trials found a statistically significant benefit favoring metformin; 1 trial found a smaller magnitude of effect (−0.14%) than the other 2 trials (−0.33% and −0.47%). A fourth trial found no difference in HbA1c at 52 weeks between the 2 groups, but did not report a measure of variance.[62] Two trials reported the mean change in weight between the 2 groups, neither reported a measure of variance. Both found a greater weight loss with metformin compared with sitagliptin, the between group differences were 1.3 kg and 1.2 kg.[61,62]

The trial by Goldstein et al. includes extension studies reporting efficacy outcomes over 52 and 104 weeks.[70,71] These data are limited by high attrition and possible contamination due to the high percentage of patients who received a sulfonylurea for HbA1c >7.5% after week 54. Overall the extension trials found that improvements in glycemic control were sustained. Data for these extension trials are provided in the Evidence Tables published as a separate document.

Saxagliptin compared with uptitrated metformin

Two trials compared saxagliptin 5 mg to metformin.[64,65] Both enrolled patients who were not at goal on submaximal dosages of metformin (extended release [XR] formulation in the Fonseca et al. study,[64] and the immediate release [IR] formulation in the Hermans et al. study[65]). Patients were randomized to receive either the addition of saxagliptin 5 mg to metformin or uptitration of metformin from 1,500 mg daily to 2,000 mg daily.

Our meta-analysis (2 trials; n=1,677) found no difference between the addition of saxagliptin 5 mg and the uptitration of metformin for reduction in HbA1c over 18 to 24 weeks (WMD −0.31, 95% CI −0.74% to 0.13, I^2=85%). The 2 trials found inconsistent results. The trial by Fonseca et al., the addition of saxagliptin 5 mg was more efficacious in reducing mean HbA1c compared with uptitrating metformin (between-group difference: −0.53, 95% CI −0.74 to −0.32).[64] In the trial by Hermans et al., there was no difference in the mean HbA1c change from baseline (between-group difference: −0.09, 95% CI −0.26 to 0.08).[65] The heterogeneity in findings could be due to differences in included populations: the trial Fonseca et al. was conducted primarily in a Hispanic population (67%), while the trial by Hermans et. al included a population that was 99% white.

One trial reported changes in weight.[64] The uptitration of metformin was associated with a greater reduction in weight compared with adding saxagliptin 5 mg (between-group difference: −0.9 kg, 95% CI −0.24 to −1.56).

GLP-1 analogs compared with metformin

Overview

Three trials compared a GLP-1 analog with metformin. In 1 trial, participants received either exenatide 10 µg twice daily or metformin 1,000 mg to 1,500 mg daily,[66] 1 trial compared exenatide XR 2 mg weekly to metformin 2,000 mg daily,[51] and 1 compared dulaglutide 0.75 mg or 1.5 mg to metformin 1,500 to 2,000 mg.[36] Study duration was 24 weeks in 2 trials and 52 weeks in the third (with primary analysis at 26 weeks).[36] Patients in 2 trials were not taking other medications for diabetes at baseline,[51,66] while patients in the other trial were either drug naïve or receiving low-dose monotherapy.[36] Mean ages ranged from 37 to 56 years and 33% to 58% of participants were women. Two trials were rated as fair-quality,[51,66] while the third was rated as good-quality.[36]

Exenatide compared with metformin

One trial (n=59) set in China compared exenatide 10 µg twice daily to metformin over 26 weeks.[66] No health outcomes were reported. Exenatide was more efficacious in reducing mean HbA1c (−2.10%; SD 1.79) compared with metformin 500 mg twice daily (−1.66%; SD 1.38), P=0.045.[66] Treatment with exenatide resulted in greater weight loss than metformin; −5.8 kg (SD 1.66) vs. −3.81 kg (SD 1.38) respectively, P<0.01.[66]

Exenatide XR compared with metformin

One trial (n=820) compared exenatide XR 2 mg weekly to metformin 2000 mg per day over 26 weeks.[51] There was no difference between exenatide XR and metformin for reducing HbA1c over 26 weeks (exenatide XR −1.53% [SE 0.07] compared with metformin −1.48% [SE 0.07]; P=0.62). No difference was found in weight loss between the 2 groups; both groups experienced a mean weight loss of 2 kg from baseline (P=0.892).[51]

Dulaglutide compared with metformin

One trial (n=807) compared dulaglutide 0.75 mg or 1.5 mg to metformin 1,500-2,000 mg over 26 weeks, with extension to 52 weeks.[36] Both dulaglutide 0.75 mg and 1.5 mg were associated with greater reduction in HbA1c compared with metformin (least-square mean change −0.15%, P=0.020 and −0.22%, P=0.002, respectively). Results were similar at 52 weeks. Likewise, the proportion of patients achieving HbA1c <7% was greater in patients receiving dulaglutide 0.75 mg (63%) and 1.5 mg (62%) than metformin (54%) (P=0.02 for both comparisons). Body weight decreases were similar between dulaglutide 1.5 mg and metformin, while body weight decreased less in patients receiving dulaglutide 0.75 mg compared to metformin at 26 weeks (−1.36 kg vs. −2.22 kg; P=0.003) and 52 weeks (P=0.001).

SGLT2 inhibitors compared with metformin

Study characteristics

Six trials compared SGLT2 inhibitors with metformin: 3 compared dapagliflozin, 2 compared empagliflozin, and 1 compared canagliflozin (Table 5). Two trials compared dapagliflozin with metformin XR 2,000 mg over 24 weeks; 1 evaluated dapagliflozin at 5 mg and the second

evaluated dapagliflozin at 10 mg, both trials were reported in 1 publication.[68] In both trials by Henry et.al, patients randomized to metformin started at 500 mg, and the dose was uptitrated to a maximum of 2,000 mg over the initial 8 week study period. The other trial compared dapagliflozin at 2 doses (5 mg and 10 mg) with metformin XR 1,500 mg over 12 weeks;[67] similarly, in this trial, patients were started at a lower dose of metformin XR (750 mg), which was uptitrated to 1,500 mg during the study period. Two trials compared empagliflozin 10 mg or 25 mg to metformin; patients in 1 trial were on background sulfonylureas,[14] while patients in the other study were drug naïve.[40] One trial compared canagliflozin 100 mg or 300 mg with metformin in drug-naïve patients.[30] This trial also assessed canagliflozin and metformin combination therapy, which is reported in the fixed-dose combination section of the report. Mean ages ranged from 52 to 59 years; approximately half of participants were women. All trials were rated as fair-quality.

Dapagliflozin compared with metformin

Our meta-analyses found that dapagliflozin (at both 5 and 10 mg) was associated with greater reduction in HbA1c than metformin XR 1,500 mg to 2,000 mg daily. However, the difference between groups was small, and not within a range generally considered to be a clinically significant change in HbA1c. For dapagliflozin 5 mg compared with metformin XR (2 trials; n=505), the WMD was −0.12% (95% CI −0.15 to −0.08), and for dapagliflozin 10 mg compared with metformin XR (2 trials; n=522), the WMD was −0.11% (95% CI −0.11 to −0.05).[67,68] In the 2 trials led by Henry et al., no difference was found for reduction in HbA1c between dapagliflozin (at either dose) and metformin XR 2,000 mg daily over 26 weeks.[68] The trial by List et al. was shorter in duration (12 weeks); patients randomized to metformin were started at a dose of 750 mg, which was titrated to 1,500 mg at week 2.[67]

Our meta-analysis (2 trials; n=505) found that dapagliflozin 5 mg was associated with greater weight loss than metformin XR 1,500 mg to 2,000 mg daily (WMD −1.18 kg, 95% CI −1.86 to −0.26); similarly, dapagliflozin 10 mg was associated with a greater weight loss than metformin XR 1,500 mg to 2,000 mg daily (WMD −1.3 kg, 95% CI −1.8 to −0.7).

Empagliflozin compared with metformin

Two trials (in 3 publications; n=336 and 660) compared empagliflozin 10 mg or 25 mg with metformin.[14,18,40] One trial was conducted in Japan over 52 weeks,[14] while the other trial was conducted in an international setting over 12 weeks, with a 78 week open-label extension.[18,40] No differences in mean HbA1c change (−0.93% vs. −0.96% vs. −0.97% at 52 weeks in 1 trial and −0.50% vs. −0.60% vs. −0.70% at 12 weeks and −0.34% vs. −0.47% vs. −0.56% at 90 weeks and in the other trial for empagliflozin 10 mg, empagliflozin 25 mg, and metformin, respectively) or the proportion of patients achieving an HbA1c <7% were reported between groups in either trial. Reductions in body weight were greater with empagliflozin 10 mg (−2.3 kg) and 25 mg (−2.8 kg) than metformin (−0.1 kg) in the longer trial (both $P<0.001$)[14]; while the difference was only significant for empagliflozin 25 mg in the shorter trial, weight reduction in the extension was greater with empagliflozin 25 mg (−2.6 kg) and empagliflozin 10 mg (−2.2 kg) compared to metformin (−1.3 kg).[40]

Canagliflozin compared with metformin

One trial (n=1,186) compared canagliflozin 100 mg and 300 mg with metformin over 26 weeks.[30] Mean reduction in HbA1c did not differ between canagliflozin 100 mg (−1.37%;

treatment difference −0.06, 95% CI −0.26 to 0.13) or 300 mg (−1.42%; treatment difference −0.11, 95% CI −0.31 to 0.08) and metformin (−1.30%). Similarly, the proportion of patients achieving HbA1c <7% did not significantly differ between canagliflozin 100 mg (39%) or 300 mg (43%) and metformin (43%). Body weight reductions were greater with canagliflozin 100 mg (−2.8 kg; treatment difference −0.9 kg, 95% CI −1.6 to −0.2 kg) and 300 mg (−3.7 kg; treatment difference −1.8 kg, 95% CI −2.6 to −1.1 kg) compared to metformin (−1.9 kg).

IV. Fixed-dose Combination Products (FDCPs) or Dual Therapy

Key Findings

- Five trials compared either an FDCP or dual therapy with a DPP-4 inhibitor and metformin with the individual components. No trials reported a health outcome as a primary outcome; evidence was general insufficient to determine whether FDCP or dual therapy led to improved health outcomes compared with component monotherapy.
- One trial (n=654) of Oseni® (FDCP of alogliptin plus pioglitazone) found greater reduction in HbA1c and greater proportion of patients achieving an HbA1c <7% with combination therapy compared to component monotherapy over 26 weeks (strength of evidence: low). Patients gained more weight with higher-dose combination therapy than monotherapy (strength of evidence: low).
- Kazano® (FDCP of alogliptin plus metformin) was more efficacious in reducing HbA1c than monotherapy for all dose comparisons; between-group differences ranged from −0.44% to −0.99%, $P<0.001$ for all comparisons (strength of evidence: moderate).
- Greater reduction in weight was seen with Kazano® 12.5 mg/1,000 mg twice daily than component monotherapy with alogliptin 12.5 mg twice daily: −1.16 kg ($P<0.003$), moderate strength of evidence. Weight changes were similar across all other groups (strength of evidence: moderate).
- Two trials (n=287 and 316) found greater reduction in HbA1c with linagliptin plus metformin dual therapy than with component monotherapy over 24 weeks (−0.70%, 95% CI −0.98% to −0.42% for 1,000 mg metformin and −1.10%; 95% CI −1.38% to −0.82% for 2,000 mg metformin in 1 study and −0.8%, 95% CI −1.1% to −0.5% for 1,500 mg to 2,000 mg metformin in the other); results were similar compared to metformin monotherapy (strength of evidence: moderate).
- Linagliptin 5 mg plus metformin 1,000 to 2,000 mg daily was not associated with differences in weight change compared to linagliptin monotherapy in one study (−0.30 kg, 95% CI −0.89 to 0.29), while significantly more weight reduction was observed with combination therapy in the other study (treatment difference −1.31 kg, 95% CI −2.18 kg to −0.44 kg) (strength of evidence: low). The group receiving linagliptin 5 mg daily plus metformin 1,000 mg had a small but statistically significant weight gain compared to patients receiving metformin 1,000 mg daily (0.60 kg, 95% CI 0.01 to 1.19). No other groups experienced a significant change in weight (strength of evidence: low).
- Two trials assessed dual therapy with sitagliptin plus metformin. One compared dual therapy to monotherapy with metformin (but not a sitagliptin arm). Our meta-analysis (2 trials; n=1,478) found greater reduction in HbA1c with sitagliptin 100 mg plus metformin 2,000 mg over 18 to 24 weeks compared with metformin monotherapy (WMD −0.60%, 95% CI −0.75 to −0.45). In 1 trial, greater reduction in HbA1c was found with dual

therapy (both dosages of metformin plus sitagliptin) than with component monotherapy at 24 weeks, and in a 30 and 52-week extension period (range −0.4% to −1.2%).

- Two trials found no difference in weight change between sitagliptin plus metformin and component monotherapy. In 1 trial, sitagliptin plus metformin 200 mg was associated with greater weight loss than metformin alone at 18 weeks (between-group difference: −1.6 kg, 95% CI −2.1 to −1.1). The second trial found a similar reduction in weight with both dosages of sitagliptin plus metformin (−0.7 kg to −1.7 kg), metformin monotherapy (−1.0 kg to −1.7 kg), and sitagliptin (−0.8 kg) over 26 weeks.
- One trial (n=1,186) of canagliflozin plus metformin compared to component monotherapy found that dual therapy was superior in mean reduction in HbA1c (canagliflozin 100 mg plus metformin vs. metformin: treatment difference −0.46%, 95% CI −0.66% to −0.27%; canagliflozin 300 mg plus metformin vs. metformin: treatment difference −0.48%, 95% CI −0.67% to −0.28%; canagliflozin 100 mg plus metformin vs. canagliflozin 100 mg: treatment difference −0.40%, 95% CI −0.59% to −0.21%; canagliflozin 300 mg plus metformin vs. canagliflozin 300 mg: treatment difference −0.36%, 95% CI −0.56% to −0.17%). The proportion of patients achieving an HbA1c <7% was significantly greater in the higher dose of dual therapy compared to metformin (56.8% vs. 43.0%; RR 1.32, 95% CI 1.10 to 1.59) but not for the lower dose of dual therapy (49.6% vs. 43%; RR 1.16, 95% CI 0.95 to 1.41); dual therapy superior to canagliflozin monotherapy at canagliflozin doses of 100 mg (49.6% vs. 38.8%; RR 1.28, 95% CI 1.05 to 1.57) and 300 mg (56.8% vs. 42.8%; RR 1.32, 95% CI 1.11 to 1.60) (strength of evidence: low). Weight change was also significantly reduced with dual therapy compared to monotherapy (canagliflozin 100 mg plus metformin vs. metformin: treatment difference −1.2 kg, 95% CI −1.9 kg to −0.6 kg; canagliflozin 300 mg plus metformin vs. metformin: treatment difference −2.0 kg, 95% CI −2.6 kg to −1.3 kg) (strength of evidence: low).
- Two trials (n=667 and 686) found dual therapy with empagliflozin plus linagliptin to be superior to component monotherapy in mean reduction in HbA1c, the proportion of patients achieving HbA1c <7%, and mean weight reduction in drug-naïve patients and patients on background metformin therapy (strength of evidence: moderate).

Overview

Four trials from the prior report and 4 newly identified trials compared either an FDCP or dual therapy with the individual components (Table 6). For this report, dual therapy was defined as using the individual components of an FDCP in separate pills/tablets. Studies were required to randomize subjects to the components of an FDCP or to monotherapy with 1 of the components of the FDCP to be eligible for this report. Studies continuing a 'background' therapy (e.g., with metformin) and randomizing subjects to add-on 1 medication (e.g., saxagliptin) or to add-on placebo were classified as comparing that medication (e.g., saxagliptin) with placebo. We excluded these placebo comparisons from this updated report.

Table 6. Characteristics of included studies: fixed-dose combination products or dual therapy

Author, Year Trial Name	Arm Dose, mg/day (N)	Follow-up (weeks)	Back-ground Therapy	Quality
Included in the prior report				
Haak, 2012[59,72]	LINA 5 mg (142) MET 1,000 mg (144) MET 2000 mg (147) LINA 5 mg + MET 1,000 mg (143) LINA 5 mg + MET 2000 mg (143)	24, 54	None	Fair
Pratley, 2014[60]	ALO 25 mg[a] (112) ALO 25 mg[b] (113) MET 1,000 mg (114) MET 2000 mg (111) ALO 25 mg + MET 1,000 mg (111) ALO 25 mg + MET 2000 mg (114)	26	None	Fair
Goldstein, 2007[63] Williams-Herman, 2009[70] Williams-Herman, 2010[71]	SITA 100 mg (179) MET 1,000 mg (82) MET 2000 mg (182) SITA 100 mg+ MET 1,000 mg (190) SITA 100 mg+ MET 1,000 mg (182)	24, 54, 104	None	Fair
Reasner, 2011[73]	SITA 100 mg +MET 2000 mg FDCP (626) MET 2000 mg (624)	18	None	Fair
New studies				
DeFronzo, 2015[16]	EMPA 25 mg + LINA 5 mg (137) EMPA 10 mg + LINA 5 mg (136) EMPA 25 mg (141) EMPA 10 mg (140) LINA 5 mg (132)	24, 52	Metformin	Fair
Lewin, 2015[23]	EMPA 25 mg + LINA 5 mg (137) EMPA 10 mg + LINA 5 mg (136) EMPA 25 mg (141) EMPA 10 mg (140) LINA 5 mg (132)	24, 52	Metformin	Fair

Author, Year Trial Name	Arm Dose, mg/day (N)	Follow-up (weeks)	Back-ground Therapy	Quality
Rosenstock, 2016[30]	CANA 100 mg + MET (237) CANA 300 mg + MET (237) CANA 100 mg (237) CANA 300 mg (238) MET (237)	26	None	Fair
Ross, 2015[34]	LINA 5 mg + MET 1,500-2,000 mg (159) LINA 5 mg (157)	24	None	Good
Rosenstock, 2010[74]	ALO 12.5 mg + PIO 30 mg (163) ALO 25 mg + PIO 30 mg (164) ALO 25 mg (164) PIO 30 mg (163)	26	None	Fair

Abbreviations: %F, percent female; %W, percent white; ALO, alogliptin; CANA, canagliflozin; EMPA, empagliflozin; LINA, linagliptin; MET, metformin; mg, milligrams; N, number; PIO, pioglitazone; SITA, sitagliptin
[a] Patients in this group were randomized to alogliptin 12.5 mg twice daily.
[b] Patients in this group were randomized to alogliptin 25 mg once daily.

Six of the 9 FDCP or dual therapy studies included metformin with alogliptin,[60] linagliptin,[34,59] sitagliptin,[63,73] or canagliflozin[30]; the remaining studies assessed the fixed-dose combination of empagliflozin and linagliptin (2 studies[16,23]) and the fixed-dose combination of alogliptin and pioglitazone.[74] In the 2 trials assessing dual therapy or FDCP of sitagliptin plus metformin, 1 compared dual therapy with both sitagliptin and metformin,[63] and the other trial compared dual therapy with metformin but not sitagliptin.[73] Mean ages ranges from 49 to 57 years. Women made up a minority in 4 trials.[16,23,59,73] Across all trials, patients were not taking additional (i.e., background) medication for diabetes, with the exception of 1 trial in which patients were taking metformin as background therapy.[16] One trial was rated good-quality; the remainders were rated fair-quality.

Detailed Assessment

Oseni® or dual therapy with alogliptin plus pioglitazone

One trial (n=654) compared dual therapy with alogliptin 12.5 mg or 25 mg plus pioglitazone 30 mg to monotherapy with alogliptin 25 mg or pioglitazone 30 mg over 26 weeks.[74] Participants were drug-naïve prior to entering the study.

Both doses of combination therapy were superior in reducing HbA1c to pioglitazone monotherapy (–1.56% for alogliptin 12.5 mg plus pioglitazone 30 mg and –1.71% for alogliptin 25 mg plus pioglitazone 30 mg vs. –1.15% for pioglitazone 30 mg; $p<0.05$ for both), while only the higher-dose combination was superior to alogliptin monotherapy (–0.96%). Likewise, the proportion of patients achieving an HbA1c <7% was significantly higher for both doses of combination therapy compared with pioglitazone monotherapy (53% for alogliptin 12.5 mg plus pioglitazone 30 mg and 63% for alogliptin 25 mg plus pioglitazone 30 mg vs. 34% for pioglitazone monotherapy, with corresponding RRs of 1.58, 95% CI 1.22 to 2.05 and RR 1.86, 95% CI 1.46 to 2.38), while only the higher-dose combination therapy was superior to alogliptin monotherapy (63% vs. 24%; RR 2.58, 95% CI 1.92 to 3.46).

Weight change differed in patients receiving combination therapy compared to monotherapy, with weight gain of 2.51 kg in the alogliptin 12.5 mg plus pioglitazone 30 mg group and 3.14 kg in the alogliptin 25 mg plus pioglitazone 30 mg compared to gain of 2.19 kg in the pioglitazone monotherapy group and weight loss of –0.29 kg in the alogliptin monotherapy group ($p<0.05$ for the higher-dose combination therapy vs. either component monotherapy).

Kazano® or dual therapy with alogliptin plus metformin

One trial (n=784) compared 2 doses of Kazano® (12.5/500 mg twice daily and 12.5/1,000 mg twice daily) to various doses of its component monotherapies (alogliptin 25 mg once daily, alogliptin 12.5 mg twice daily, metformin 500 mg twice daily, metformin 1,000 mg twice daily)[60] over 26 weeks. Participants were treatment naïve prior to entering the study.

Both Kazano 12.5/500 mg twice daily and 12.5/1,000 mg twice daily were more efficacious than component monotherapies in reducing mean HbA1c: alogliptin 25 mg daily: −0.52%, alogliptin 12.5 mg twice daily: −0.56% [SE 0.093], metformin 500 mg twice daily: −0.65% [SE 0.094], metformin 1,000 mg twice daily: −1.11% [SE 0.092], Kazano® 12.5/500 twice daily: −1.22% [SE 0.094], Kazano® 12.5/1,000 mg twice daily: −1.55% [SE 0.090]; $P < 0.001$ for all comparisons of combination therapy compared with component monotherapies.

Kazano® 12.5/1,000 mg twice daily resulted in greater weight loss than treatment with alogliptin 12.5 mg twice daily alone (−1.17 kg [SE 0.268] compared with −0.01 kg [SE 0.288]; $P=0.003$). No difference in weight was found between the remaining comparators (alogliptin 25 mg daily: 0.13 kg, metformin 500 mg twice daily: −0.80 kg [SE 0.283], metformin 1,000 mg twice daily: −1.25 kg [SE 0.270], Kazano® 12.5/500 twice daily: −0.57 kg [SE 0.28]).

Jentadueto® or dual therapy with linagliptin plus metformin

Two trials compared dual therapy with linagliptin plus metformin to each component monotherapy over 24 weeks[34,59]; 1 trial also had an optional extension trial to 54 weeks.[72] In the previously included trial, participants were randomized to 1 of 2 combinations of linagliptin 2.5 mg twice daily combined with metformin at either 500 mg or 1,000 mg twice daily, or the respective monotherapies. At both doses, dual therapy was more efficacious than component monotherapies. The mean change from baseline HbA1c with dual therapy compared with each component is as follows: −0.70% (95% CI −0.98 to −0.42) for linagliptin 2.5 mg twice daily plus metformin 500 mg twice daily compared with linagliptin 5 mg once daily; −0.60% (95% CI −0.88 to −0.32) for linagliptin 2.5 mg twice daily plus metformin 500 mg twice daily compared with metformin 500 mg twice daily; −1.10% (95% CI −1.38 to −0.82) for linagliptin 2.5 mg twice daily plus metformin 1,000 mg twice daily compared with linagliptin 5 mg daily; and −0.50% (95% CI −0.78 to −0.22) for linagliptin 2.5 mg twice daily plus metformin 1,000 mg twice daily compared with metformin 1,000 mg twice daily.[59]

In the extension trial, patients initially randomized to either metformin 500 mg or linagliptin 5 mg were reallocated to another arm; patients participating in the extension trial who continued in the original randomized groups were analyzed separately (e.g., “non-switched” groups).[72] No further reduction in HbA1c or weight occurred over 24 to 54 weeks. Across all groups, the mean change in HbA1c from 26 to 54 weeks ranged from 0.12% to 0.33% across both dual therapy groups and those taking metformin 100 mg twice daily.

No difference was seen in the mean weight change from baseline in patients receiving linagliptin 2.5 mg twice daily plus metformin 500 mg twice daily compared with linagliptin 5 mg (−0.30 kg, 95% CI −0.89 to 0.29) or between the groups receiving linagliptin 2.5 mg twice daily

plus metformin 1,000 mg twice daily compared with metformin 1,000 mg twice daily (−0.30 kg, 95% CI −0.89 to 0.29). Patients receiving linagliptin 2.5 mg twice daily plus metformin 1,000 mg twice daily experienced greater weight loss than those receiving linagliptin 5 mg daily (−1.00 kg, 95% CI −1.59 to −0.41). Linagliptin 2.5 mg twice daily plus metformin 500 mg twice daily was associated with a small but statistically significant weight gain compared to patients receiving metformin 500 mg twice daily (0.60 kg, 95% CI 0.01 to 1.19).[59]

The newly identified trial (n=316) compared dual therapy with linagliptin 5 mg and metformin 1,500 to 2,000 mg daily with linagliptin monotherapy over 24 weeks.[34] Dual therapy was superior to linagliptin monotherapy in mean reduction of HbA1c (−2.8% vs. −2.0%; treatment difference −0.8%, 95% CI −1.1% to −0.5%) and in the proportion of patients achieving an HbA1c <7% (61% vs. 40%; RR 1.52, 95% CI 1.21 to 1.91). Further, change in body weight was significantly greater for the dual therapy group compared to monotherapy (−1.07 kg vs. 0.24 kg; treatment difference −1.31 kg, 95% CI −2.18 kg to −0.44 kg).

Janumet® or dual therapy with sitagliptin plus metformin

Two trials compared sitagliptin plus metformin to at least 1 component monotherapy.[63,73] One 24 week trial[63] with an optional additional 30 weeks[70] and further additional 50 week extension[71] (Table 6) compared initial dual therapy of sitagliptin plus metformin to sitagliptin monotherapy and metformin monotherapy. Patients were followed initially for 24 weeks, and then had the option to continue for 30 additional weeks and then an additional 50 weeks. In the second trial, patients received sitagliptin 50 mg plus metformin 500 mg twice daily in an FDCP twice daily (uptitrated to sitagliptin 50 mg plus metformin 1,000 mg twice daily) or metformin 500 mg twice daily (uptitrated to 1,000 mg twice daily) over 18 weeks; there was no arm that received sitagliptin monotherapy.[73] Our meta-analysis (2 trials) found that sitagliptin 100 mg plus metformin 2000 mg per day was more efficacious in reducing mean HbA1c over 18 to 24 weeks compared with metformin monotherapy (WMD −0.60%, 95% CI −0.75 to −0.45). Additional results from the trial by Goldstein et al. for the extension studies are provided in the Evidence Tables; as mentioned previously, this data is limited by high attrition and contamination due to multiple participants receiving a sulfonylurea for HbA1c >7.5% after week 54. Across all outcome timings, dual therapy with sitagliptin plus metformin was more efficacious than component monotherapy. In 1 trial, sitagliptin plus metformin was associated with greater weight loss than metformin alone at 18 weeks (between-group difference: −1.6 kg, 95% CI −2.1 to −1.1).[73] The second trial found a similar reduction in weight with both dosages of sitagliptin plus metformin, (−0.7 kg to −1.7 kg), metformin monotherapy (−1.0 kg to −1.7 kg), and sitagliptin (−0.8 kg) over 26 weeks.[63]

Invokamet® or dual therapy with canagliflozin plus metformin

One trial (n=1,186) compared dual therapy with canagliflozin 100 mg or 300 mg plus metformin XR to component monotherapy over 26 weeks.[30] Dual therapy was superior to component monotherapy in mean reduction in HbA1c (canagliflozin 100 mg plus metformin vs. metformin: treatment difference −0.46%, 95% CI −0.66% to −0.27%; canagliflozin 300 mg plus metformin vs. metformin: treatment difference −0.48%, 95% CI −0.67% to −0.28%; canagliflozin 100 mg plus metformin vs. canagliflozin 100 mg: treatment difference −0.40%, 95% CI −0.59% to −0.21%; canagliflozin 300 mg plus metformin vs. canagliflozin 300 mg: treatment difference −0.36%, 95% CI −0.56% to −0.17%). The proportion of patients achieving an HbA1c <7% was significantly greater in the higher dose of dual therapy compared to metformin (56.8% vs.

43.0%; RR 1.32, 95% CI 1.10 to 1.59) but not for the lower dose of dual therapy (49.6% vs. 43%; RR 1.16, 95% CI 0.95 to 1.41); dual therapy was superior to canagliflozin monotherapy at canagliflozin doses of 100 mg (49.6% vs. 38.8%; RR 1.28, 95% CI 1.05 to 1.57) and 300 mg (56.8% vs. 42.8%; RR 1.32, 95% CI 1.11 to 1.60).

Body weight was also significantly reduced with dual therapy compared to monotherapy (canagliflozin 100 mg plus metformin vs. metformin: treatment difference −1.2 kg, 95% CI −1.9 kg to −0.6 kg; canagliflozin 300 mg plus metformin vs. metformin: treatment difference −2.0 kg, 95% CI −2.6 kg to −1.3 kg).

Comparisons of canagliflozin monotherapy with metformin are reported in the metformin comparison section above.

Glyxambi® or dual therapy with empagliflozin plus linagliptin

Two trials[16,23] (n=677 and 686) compared dual therapy with empagliflozin plus linagliptin to component monotherapy over 52 weeks (with the primary endpoint at 24 weeks); 1 study was conducted in drug-naïve patients,[23] while the other was conducted in patients whose diabetes was inadequately controlled on metformin monotherapy.[16] In drug-naïve patients, mean reduction in HbA1c at 24 weeks was greater with empagliflozin 25 mg plus linagliptin 5 mg (−1.08%) compared with linagliptin 5 mg monotherapy (−0.67%; treatment difference −0.41%, 95% CI −0.61% to −0.22%) but not with empagliflozin monotherapy (−0.95; treatment difference −0.14%, 95% CI −0.33% to 0.06%); mean reduction in HbA1c was greater for empagliflozin 10 mg plus linagliptin 5 mg (−1.24) than both individual components (−0.83 for empagliflozin 10 mg, treatment difference −0.41%, 95% CI −0.61% to −0.21%; and −0.67 for linagliptin 5 mg, treatment difference −0.57%, 95% CI −0.76% to −0.37%). Efficacy was maintained at 52 weeks. The proportion of patients achieving an HbA1c <7% was greater with empagliflozin 25 mg plus linagliptin 5 mg compared to empagliflozin monotherapy (OR 1.9, 95% CI 1.1 to 3.3) or linagliptin monotherapy (OR 3.1, 95% CI 1.8 to 5.3). Similarly, proportions of patients achieving an HbA1c <7% were greater for empagliflozin 10 mg plus linagliptin 5 mg dual therapy compared to empagliflozin monotherapy (OR 3.0, 95% CI 1.7 to 5.2) or linagliptin monotherapy (OR 4.3, 95% CI 2.5 to 7.5). Changes in body weight were significantly greater for empagliflozin 25 mg plus linagliptin 5 mg compared to linagliptin monotherapy (−2.0 kg vs. −0.8 kg; treatment difference −1.2 kg, 95% CI −2.2 kg to −0.2 kg) but not empagliflozin monotherapy (−2.0 kg vs. −2.1 kg; treatment difference 0.1 kg, 95% CI −0.9 kg to 1.1 kg); similarly, empagliflozin 10 mg plus linagliptin 5 mg resulted in greater reductions in body weight than linagliptin monotherapy (−2.7 kg vs. −0.8 kg; treatment difference −2.0 kg, 95% CI −3.0 to −1.0 kg) but not empagliflozin monotherapy (−2.7 kg vs. −2.3 kg; treatment difference −0.5 kg, 95% CI −1.5 kg to 0.5 kg).

In patients with diabetes inadequately controlled by metformin monotherapy, dual therapy was associated with greater mean reduction in HbA1c than component monotherapy[16]; empagliflozin 25 mg plus linagliptin 5 mg was superior to empagliflozin monotherapy (−1.19% vs. −0.62%; treatment difference −0.58%, 95% CI −0.75% to −0.41%) and linagliptin monotherapy (−1.19% vs. −0.70%; treatment difference −0.50%, 95% CI −0.67% to −0.32%), as was empagliflozin 10 mg plus linagliptin 5 mg (−1.08% vs. −0.66% vs. −0.70%; treatment difference vs. empagliflozin monotherapy −0.42%, 95% CI −0.59% to −0.25%; treatment difference vs. linagliptin monotherapy −0.39%, 95% CI −0.56% to −0.21%). Likewise, the proportion of patients achieving an HbA1c <7% was significantly greater for dual therapy compared to monotherapy, with rates of 61.8% of patients receiving empagliflozin 25 mg plus

linagliptin 5 mg compared to 32.6% of patients receiving empagliflozin monotherapy (OR 4.2, 95% CI 2.3 to 7.6) and 36.1% of patients receiving linagliptin monotherapy (OR 3.5, 95% CI 1.9 to 6.4), and rates of 57.8% of patients receiving empagliflozin 10 mg plus linagliptin 5 mg compared to 28.0% of patients receiving empagliflozin monotherapy (OR 2.8, 95% CI 1.6 to 5.0) and 36.1% of patients receiving linagliptin monotherapy (OR 4.5, 95% CI 2.5 to 8.2). Compared with linagliptin monotherapy (−0.7 kg), mean reduction in body weight was significantly greater for empagliflozin 25 mg plus linagliptin 5 mg (−3.0 kg; treatment difference −2.3 kg, 95% CI −3.2 kg to −1.4 kg) and empagliflozin 10 mg plus linagliptin 5 mg (−2.6 kg; treatment difference −1.9 kg, 95% CI −2.8 kg to −1.1 kg); differences were not significant compared to empagliflozin monotherapy.

Key Question 2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with type 2 diabetes mellitus?

I. Intra-class Comparisons (within a class)

Key Findings: Harms

DPP-4 inhibitors

- In 2 trials, there were no differences in rates of adverse events (45% vs. 45%; pooled RR 0.99, 95% CI 0.86 to 1.14; I^2=0%) or withdrawals from adverse events (2.1% vs. 2.0%; pooled RR 1.08, 95% CI 0.45 to 2.59; I^2=0%) between groups over 18 or 24 weeks (strength of evidence: low).
- Overall, 24 people experienced hypoglycemia, 13 (3.2%) in the saxagliptin group and 11 (2.8%) in the sitagliptin group. Most of the hypoglycemic events were considered mild; there were 3 major hypoglycemic events in the sitagliptin group.

GLP1-analogs

- In 1 trial, rates of withdrawal due to adverse events were similar between groups over 26 weeks (strength of evidence: low).
- Three trials compared exenatide 2 mg once weekly with exenatide 10 µg twice daily over 24 to 30 weeks. Our meta-analysis found no difference between groups for rates of withdrawals due to adverse events (3 trials, n=1,223, RR 0.72, 95% CI 0.35 to 1.50) (strength of evidence: low)
- One trial (n=976) compared exenatide with dulaglutide, reporting no differences between groups for overall adverse events (77% vs. 71% vs. 72%; dulaglutide 0.75 mg, RR 0.99, 95% CI 0.89 to 1.10; dulaglutide 1.5 mg, RR 1.07, 95% CI 0.97 to 1.18) (strength of evidence: low). Gastrointestinal events were less frequent with dulaglutide 0.75 mg compared to exenatide (34% vs. 46%; RR 0.72, 95% CI 0.59 to 0.89), but there was no difference in rates of gastrointestinal events between dulaglutide 1.5 mg and exenatide (51% vs. 46%; RR 1.10, 95% CI 0.92 to 1.30) (strength of evidence: low).
- One trial (n=599) compared dulaglutide with exenatide, reporting no difference in rates of gastrointestinal events (36% vs. 36%; RR 1.00, 95% CI 0.81 to 1.24) (strength of evidence: low).

- One trial (n=841) compared albiglutide to liraglutide, reporting no differences between groups were reported for overall adverse events (76% vs. 78%; RR 0.97, 95% CI 0.90 to 1.05) (strength of evidence: low).

Overview

We included 5 fair-quality trials from the prior report and 5 newly identified fair-quality trials comparing drugs within the same class for Key Question 2. Two trials compared saxagliptin with sitagliptin;[24,44] the other 8 trials compared two different GLP-1 analogs.[17,28,32,37,45-48] Details of the study characteristics for these 10 trials are presented in Table 3 in the corresponding section of Key Question 1 and in the Evidence Tables (included in a separate file). We rated 1 additional trial comparing different GLP-1 analogs poor for harms outcomes and did not include it in this section or the tables.[49] We found no trials assessing intra-class comparisons of amylin agonists or SGLT2 inhibitors.

Detailed Assessment of for Intra-class Comparisons: Harms

DPP-4 Inhibitors

Sitagliptin compared with saxagliptin

Two trials compared sitagliptin 100 mg once daily with saxagliptin 5 mg once daily in adults already on stable doses of 1500 mg to 3000 mg of metformin daily over 18 weeks.[24,44] There were no statistically significant differences in rates of adverse events (45% vs. 45%; pooled RR 0.99, 95% CI 0.86 to 1.14; I^2=0%) or withdrawals from adverse events (2.1% vs. 2.0%; pooled RR 1.07, 95% CI 0.44 to 2.57; I^2=0%) between the groups in either study.

In addition, 1 nested case-control study assessed risk of pancreatitis among diabetics treated with DPP-4 inhibitors compared to non-users,[15] and 1 retrospective database study assessed the association of DPP-4 inhibitor use with hospitalization for heart failure.[19] In both studies, no association was reported between DPP-4 inhibitor use and these serious adverse events.

GLP-1 Analogs

Exenatide 10 µg twice daily compared with liraglutide 1.8 mg once daily

In 1 trial (n=464) comparing exenatide 10 µg twice daily with liraglutide 1.8 mg once daily, among patients who were not adequately controlled on background therapy with metformin, a sulfonylurea, or both, withdrawal rates because of adverse events were not significantly different between groups over 26 weeks.[45] In the liraglutide arm, 10% of participants withdrew because of adverse events, compared with 13% of participants in the exenatide arm.

The incidence of nausea was similar between the groups initially, but was more persistent over time in the exenatide group. Otherwise, the distribution of adverse events was similar between the study arms. There were 2 major episodes of hypoglycemia in patients in the exenatide arm of the study who were also on a sulfonylurea. No major episodes of hypoglycemia occurred in the liraglutide arm of the study.

Exenatide XR 2 mg once weekly compared with exenatide 10 µg twice daily

Three trials included in the prior report compared exenatide 2 mg once weekly with exenatide 10 µg twice daily over 24 to 30 weeks. Our meta-analysis showed no difference between groups for rates of withdrawals due to adverse events (3 trials, n=1,223, RR 0.72, 95% CI 0.35 to 1.50) (Appendix E). In the 26-week trial, the exenatide 10 µg twice daily group had a higher rate of

withdrawal due to adverse events compared with the exenatide 2 mg once weekly group (10.4% vs. 4.4%). However, rates between the groups were similar in the other 2 trials.

Exenatide compared with dulaglutide

One trial (n=976) compared exenatide 5 µg to 10 µg twice daily with dulaglutide 0.75 mg or 1.5 mg once weekly over 52 weeks (with primary analysis at 26 weeks) in patients already on metformin and/or pioglitazone.[37] No differences between groups were reported for overall adverse events (77% vs. 71% vs. 72%; dulaglutide 0.75 mg, RR 0.99, 95% CI 0.89 to 1.10; dulaglutide 1.5 mg, RR 1.07, 95% CI 0.97 to 1.18) or withdrawal due to adverse events (3.3% vs. 1.4% vs. 2.9%; dulaglutide 0.75 mg, RR 0.88, 95% CI 0.34 to 2.25; dulaglutide 1.5 mg, RR 0.44, 95% CI 0.14 to 1.41). Gastrointestinal events were less frequent with dulaglutide 0.75 mg compared to exenatide (34% vs. 46%; RR 0.72, 95% CI 0.59 to 0.89), but there was no different in rates of gastrointestinal events between dulaglutide 1.5 mg and exenatide (51% vs. 46%; RR 1.10, 95% CI 0.92 to 1.30).

Exenatide compared with albiglutide

One trial (n=66) compared albiglutide 30 mg once weekly with exenatide 5 µg to 10 µg twice daily over 16 weeks in patients who were drug naïve or treated with metformin monotherapy only.[32] No differences between groups were reported for overall adverse events (69% vs. 84%; RR 0.82, 95% CI 0.62 to 1.07), withdrawal due to adverse events (16% vs. 3%; RR 0.18, 95% CI 0.02 to 1.44), nausea (26% vs. 40%; RR 0.51, 95% CI 0.25 to 1.04), diarrhea (16% vs. 23%; RR 0.55, 95% CI 0.20 to 1.51), or vomiting (13% vs. 17%; RR 0.59, 95% CI 0.18 to 1.90).

Dulaglutide compared with liraglutide

One trial (n=599) compared dulaglutide 1.5 mg once weekly with liraglutide 1.8 mg once daily over 26 weeks in patients on a stable dose of metformin ≥1,500 mg per day.[17] No differences between groups were reported for overall adverse events (62% vs. 63%; RR 0.98, 95% CI 0.87 to 1.11), rates of hypoglycemia (0.4 vs. 0.3 vs. 0.1 events/patient/year), withdrawal due to adverse events (6% vs. 6%; RR 1.00, 95% CI 0.53 to 1.89), or rates of gastrointestinal events (36% vs. 36%; RR 1.00, 95% CI 0.81 to 1.24).

Albiglutide compared with liraglutide

One trial (n=841) compared albiglutide 30 mg to 50 mg once weekly to liraglutide 0.6 mg to 1.8 mg once daily over 32 weeks in patients with diabetes uncontrolled by metformin, TZDs, sulfonylureas, or combination therapy.[28] No differences between groups were reported for overall adverse events (76% vs. 78%; RR 0.97, 95% CI 0.90 to 1.05), withdrawal due to adverse events (10.0% vs. 7.7%; RR 1.31, 95% CI 0.84 to 2.05), or diarrhea (15% vs. 14%; RR 1.10, 95% CI 0.78 to 1.55).

II. Between-Class Comparisons: Harms

Key Findings: Harms

DPP-4 inhibitors compared with GLP-1 analogs

- Two trials compared exenatide XR 2 mg and sitagliptin 100 mg and found low strength evidence of increased rates of study withdrawal due to adverse events with exenatide XR (4% vs. 2%, RR 2.61; 95% CI 1.03 to 6.61) but no difference in the risk of experiencing

any adverse event between the two treatments; there was also low strength evidence of increased gastrointestinal adverse events with exenatide XR.

- One Italian registry study provided low strength evidence of increased severe adverse drug reactions with exenatide compared with sitagliptin over a 30-month period (40 in 21,064 patients on exenatide vs. 20 in 38,811 patients on sitagliptin).
- Three trials provided moderate strength evidence that treatment with liraglutide 0.9 mg, 1.2 mg and 1.8 mg was associated with increased risk of experiencing any adverse event and 2 trials provided low strength evidence of increased study withdrawals due to adverse events compared with sitagliptin 100 mg (59% vs. 48%, RR 1.16; 1.05 to 1.28; 7% vs. 2%, RR 3.28; 95% CI 1.81 to 5.93, respectively); gastrointestinal adverse events were more frequent with liraglutide.
- One trial compared albiglutide 30 mg with sitagliptin 100 mg and found low strength evidence of no difference between treatments in risk of experiencing any adverse event or in study withdrawal due to adverse events; diarrhea and nausea were more common with albiglutide based on low strength evidence
- Treatment with dulaglutide resulted in a similar rates of hypoglycemic events and study withdrawals due to adverse events compared with sitagliptin 100 mg; gastrointestinal adverse events were more frequent with dulaglutide at 26 weeks: (RR 1.84, 95% CI 1.38 to 2.46) and at 104 weeks: (RR 1.44, 95% CI 1.19 to 1.74) based on low strength of evidence
- One trial provided low strength evidence of increased rate of experiencing 1 or more adverse events with liraglutide 1.2 mg compared with saxagliptin 5 mg in 136 Chinese patients poorly controlled on metformin and/or a sulfonylurea or other antidiabetic agents (51% vs. 21%; RR 2.46, 95% CI 1.43 to 4.23), but no difference between groups in withdrawal due to adverse events, although nausea was more frequent with liraglutide (27% vs. 3%; RR 8.37, 95% CI 2.02 to 35).

DPP-4 inhibitors compared with SGLT2 inhibitors

- Three trials (n=1,626) and 1 systematic review provided moderate strength evidence of no difference between treatment with canagliflozin 300 mg and sitagliptin 100 mg in risk of experiencing any adverse event (7% vs. 7%; RR 1.02, 95% CI 0.97 to 1.09) or in study withdrawals due to adverse events (5% vs. 3%; RR 1.34, 95% CI 0.86 to 2.10); there was 4 times the risk of genital mycotic infection with canagliflozin treatment than with sitagliptin (RR 4.20, 95% CI 2.51 to 7.03, moderate strength of evidence) but no difference risk of hypoglycemia (RR 1.29, 95% CI 0.82 to 2.03, low strength of evidence).
- Two trials (n=1,059) provided moderate strength of evidence of no difference between empagliflozin 25 mg and 10 mg versus sitagliptin 100 mg in rates of experiencing one or more adverse events (63% vs. 57%; RR 1.06, 95% CI 0.95 to 1.19, combined empagliflozin arms) and study withdrawals due to adverse events (2% vs. 3%; RR 0.77, 95% CI 0.31 to 1.90, combined empagliflozin arms); the risk of genital infections was 4 times greater with empagliflozin compared with sitagliptin (3.5% vs. 0.7%; RR 3.99, 95% CI 1.08 to 14, I^2=0%) but there was no difference in risk of hypoglycemia.
- Two trials provided moderate strength of evidence of no differences in risk of experiencing any adverse event (73% vs. 71%; RR 1.03, 95% CI 0.94 to 1.13, combined

empagliflozin 25 mg and 10 mg arms) or in rates of study withdrawal due to adverse events between empagliflozin and sitagliptin (5% vs. 2%; RR 1.99, 95% CI 0.83 to 4.77). However, genital infections were more likely with empagliflozin treatment than treatment with linagliptin (7% v. 3%; RR 2.50, 95% CI 1.11 to 5.47, I^2=0%) but there was no difference in risk of hypoglycemia (RR 1.43, 95% CI 0.47 to 4.36)

- One trial (n=355) provided low strength evidence of no difference in rates of experiencing any adverse event or in study withdrawals due to adverse events between dapagliflozin 10 mg and saxagliptin 5 mg. There were more genital infections with dapagliflozin than with saxagliptin (6% vs. 0.6%; RR 9.83, 95% CI 1.27 to 76).

Overview

For harms outcomes, we included the same 17 trials that were included for benefit, along with the systematic review by Yang and colleagues.[38] For harms we also included an additional observational study of exenatide and sitagliptin from an Italian registry.[26] These 19 studies compared an included drug from 1 class with an included drug from another class. There were no studies comparing a GLP-1 analog with an SGLT2 inhibitor.

Detailed Assessment for Between-class Comparisons: Harms

DPP-4 inhibitors compared with GLP-1 analogs

Sitagliptin compared with exenatide XR

Two trials (n=727) compared exenatide XR 2 mg once weekly to sitagliptin 100 mg daily over 26 weeks.[50,51] Study drugs were added on to metformin in 1 trial[50] while patients were treatment-naïve in the other.[51] The pooled analysis of withdrawal due to adverse events provided low strength evidence of increased risk with exenatide XR (4% vs. 2%; RR 2.61, 95% CI 1.03 to 6.61, I^2=0%) compared with sitagliptin. The risk of experiencing any serious adverse event was 2% in both groups (n=727, RR 0.83, 95% CI 0.37 to 1.86, I^2=0%). Neither study reported rates of having 1 or more adverse events. Both studies reported that no patient experienced any major hypoglycemic episodes. There was low strength of evidence that gastrointestinal side effects were common in both studies and occurred more frequently in patients taking exenatide XR (nausea RR 2.62, 95% CI 1.66 to 4.15; vomiting RR 3.67, 95% CI 1.63 to 8.24; diarrhea RR 1.91, 95% CI 1.22 to 3.00).

Sitagliptin compared with exenatide

One study (n=30) compared exenatide 5 µg twice daily to sitagliptin 100 mg and reported 1 patient taking exenatide withdrew after developing pancreatitis (6%) and 1 patient taking sitagliptin withdrew for alcohol abuse with transaminitis (8%).[20] Adverse events were not otherwise reported. (Strength of evidence insufficient for all outcomes)

We also identified 1 observational study comparing exenatide with sitagliptin that included 21,064 patients treated with exenatide and 38,811 patients treated with sitagliptin. In February 2008 the Italian Medicines Agency approved reimbursed use of exenatide and sitagliptin provided patients were enrolled into a web-based registry to monitor use, safety, and efficacy. The baseline HbA1c and duration of diabetes were 8.8% and 10 years for patients treated with exenatide and 8.3% and 9.1 years for patients treated with sitagliptin. The median time to an adverse drug reaction was 2.06 months with exenatide and 2.85 months with sitagliptin. There were 40 severe adverse drug reactions with exenatide (incidence rate [IR] 2.40) including 6 cases of acute pancreatitis, 7 cases of severe nausea and vomiting, and four cases of

renal failure during the following 30 months representing an IR of 0.33, 0.39, and 0.22 per 1000 person-years. There were 20 cases of severe adverse drug reactions with sitagliptin (IR 0.65) including 3 cases of acute pancreatitis corresponding to an IR 0.10/1000 person-years (exenatide vs. sitagliptin adverse drug reaction: RR 3.69, 95% CI 2.16 to 6.30; low strength of evidence). Hypoglycemia was more likely when patients were taking a sulfonylurea either alone or with metformin. The relative risk for add-on to a sulfonylurea compared to add-on therapy to metformin was 2.96 (95% CI 2.33 to 3.50) with exenatide and 2.99 (95% CI 2.45 to 3.64) on sitagliptin. Forty-six percent of patients discontinued exenatide therapy (8% for treatment failure) versus 35% (4% for treatment failure) with sitagliptin. The most common drug change was from sitagliptin to exenatide.

Sitagliptin compared with liraglutide

Two trials (n=1,410) compared treatment with liraglutide versus sitagliptin for 24 to 26 weeks.[52,53] In these trials, patients were inadequately controlled on metformin. The risk of experiencing 1 or more adverse events and study withdrawals were higher with liraglutide compared with sitagliptin (59% vs. 48%; RR 1.16, 1.05 to 1.28, I^2=0%, low strength evidence; 7% vs. 2%; RR 3.28, 95% CI 1.81 to 5.93, I^2=6%, moderate strength evidence). Evidence for hypoglycemia was mixed and considered insufficient. There was less symptomatic hypoglycemia with liraglutide based on 1 study (n=653, 4% vs. 12%; RR 0.33, 95% CI 0.18 to 0.61)[52] but no difference between treatments in rates of minor hypoglycemia based on another study (n=658, 5% vs. 5%; RR 1.15, 95% CI 0.56 to 2.37).[53] As with exenatide XR, there was low strength evidence that gastrointestinal adverse events were more frequent with liraglutide than with sitagliptin (37% vs. 21%; RR 1.75, 95% CI 1.31 to 2.32) based on 1 study that reported gastrointestinal adverse events together[53] but results were similar in the other 2 studies that reported diarrhea, nausea, and vomiting separately.

A 26-week extension (of 1 26-week study)[57] found study withdrawals due to adverse events remained increased with liraglutide (n=658, 10% vs. 3%; RR 3.14, 95% CI 1.44 to 6.85). Gastrointestinal adverse events also remained increased with liraglutide compared with sitagliptin at 1 year (40% vs. 24%; RR 1.67, 95% CI 1.28 to 2.17).

Sitagliptin compared with albiglutide

One trial (n=628) compared albiglutide 30 mg weekly with sitagliptin 100 mg daily in patients taking metformin for 104 weeks.[13] There was low strength evidence of no difference in risk of experiencing any adverse event (84% vs. 79%; RR 1.06, 95% CI 0.98 to 1.14) or in study withdrawal due to adverse events between albiglutide and sitagliptin (6% vs. 3%; RR 1.99, 95% CI 0.95 to 4.18) or in risk of having a serious adverse event (12% vs. 9%; RR 1.33, 95% CI 0.83 to 2.14). There were no severe hypoglycemic events and documented symptomatic events were few (4% vs. 2%; RR 2.20, 95% CI 0.77 to 6.26) providing low strength evidence of no difference between treatments. Upper respiratory tract infections were the most frequently occurring adverse event and was more likely in the group receiving albiglutide (19% vs. 11%; RR 1.71, 95% CI 1.15 to 2.53). Both diarrhea and nausea were more likely with albiglutide (15% vs. 9%; RR 1.64, 95% CI 1.06 to 2.56; 12% vs. 7%; RR 1.68, 95% CI 1.02 to 2.78, respectively, low strength of evidence for both outcomes).

Sitagliptin compared with dulaglutide

One fair-quality trial (n=921) compared dulaglutide 1.5 mg and dulaglutide 0.75 mg with sitagliptin 100 mg in metformin-treated patients. At 26 weeks, 52 weeks, and 104 weeks, patients given dulaglutide were more likely to experience any adverse event than those treated with sitagliptin (26 weeks: 68% vs. 59%; RR 1.16, 95% CI 1.04 to 1.29; 52 weeks: 77% vs. 70%; RR 1.10; 95% CI 1.01 to 1.20;104 weeks: 84% vs. 77%; RR 1.10, 95% CI 1.03 to 1.18)However, there were no differences in withdrawal due to adverse events after 104 weeks between dulaglutide 1.5 mg and sitagliptin (21% each treatment).. Gastrointestinal events were the most common treatment emergent adverse event at both 26 weeks and 104 weeks and occurred most frequently with dulaglutide (35% vs. 17%; RR 2.01, 95% CI 1.55 to 2.62; 43% vs. 30%; RR 1.44, 95% CI 1.19 to 1.74).[27,41] There were no severe hypoglycemic episodes reported and total hypoglycemia incidence was 13% for dulaglutide 1.5 mg, and 9% for dulaglutide 0.75 mg and sitagliptin at 104 weeks (RR 1.25, 95% CI 0.82 to 1.92 with dulaglutide arms combined; RR 1.50, 95% CI 0.94 to 2.38 dulaglutide 1.5 mg vs. sitagliptin). Evidence for adverse events was low strength for all outcomes.

Saxagliptin compared with liraglutide

One trial compared add-on therapy with liraglutide 1.2 mg or saxagliptin 5 mg in 136 Chinese patients with poorly controlled diabetes (mean baseline HbA1c 8.5% to 8.6%) on metformin and/or a sulfonylurea or other diabetic agents.[25] Patients treated with liraglutide were more likely to experience 1 or more adverse events than patients treated with saxagliptin (51% vs. 21%; RR 2.46, 95% CI 1.43 to 4.23) although there was no difference between groups in withdrawal due to adverse events (3% vs. 0%; RR 5.00, 95% CI 0.25 to 102). Nausea was more frequent with liraglutide (27% vs. 3%; RR 8.37, 95% CI 2.02 to 35). There were no differences between groups in other gastrointestinal adverse events or in risk of experiencing hypoglycemia (6% vs. 5%; RR 1.31, 95% CI 0.31 to 5.62); there were no episodes of major hypoglycemia during the study.

DPP-4 inhibitors compared with SGLT2 inhibitors

Sitagliptin compared with canagliflozin

Three trials (n=1,626)[54-56,58] and 1 systematic review[38] compared treatment with canagliflozin 100 mg and 300 mg to sitagliptin 100 mg over 12 and 52 weeks. Patients in 1 of the 52-week were on a background therapy of metformin plus sulfonylurea. Patients in the other 2 trials were taking metformin monotherapy. The risk of experiencing any adverse event was not different between canagliflozin and sitagliptin (7% vs. 7%; RR 1.02, 95% CI 0.97 to 1.09, I^2=1%; low strength of evidence). The rates of study withdrawal due to adverse events were also not different between the 2 treatments (5% vs. 3%; RR 1.34, 95% CI 0.86 to 2.10, I^2=30%; low strength of evidence). Only 1 of the 3 trials reported any gastrointestinal adverse event outcomes such as nausea or diarrhea and reported no significant differences between groups for these outcomes.[55] However, the systematic review pooled results for genital mycotic infections and found moderate strength evidence that treatment with canagliflozin 300 mg was associated with 4 times the risk compared with treatment with sitagliptin (RR 4.20; 95% CI 2.51 to 7.03).[38] while there was low strength of evidence of no difference in urinary tract infections (UTIs) or in hypoglycemia (RR 1.05, 95% CI 0.68 to 1.61; RR 1.29, 95% CI 0.82 to 2.03, respectively).[38]

Sitagliptin compared with empagliflozin

Two trials (n=1,058) compared empagliflozin 25 mg and empagliflozin 10 mg with sitagliptin 100 mg[29,33] in patients who were treatment-naïve[29] or who were inadequately controlled on metformin[33] for 24 weeks[29] or for 12 weeks[33] with a 78-week extension.[40] Most participants experienced at least 1 adverse event with empagliflozin (63%) and sitagliptin (57%), RR 1.06 (95% CI 0.95 to 1.19, I^2=0%, moderate strength of evidence). There were also moderate strength evidence of no differences between empagliflozin and sitagliptin in study discontinuations due to adverse events (2% vs. 3%, RR 0.77; 95% CI 0.31 to 1.90, I^2=0%). There were no hypoglycemic events requiring assistance in 1 trial with less than 1% experiencing hypoglycemia in each study arm discussed here;[29] similarly 2% experienced hypoglycemia in both empagliflozin arms in the other trial;[40] compared with 4% among patients treated with sitagliptin (RR 1.18; 95% CI 0.25 to 5.52) with empagliflozin arms combined (low strength of evidence). The risk of genital infections (not otherwise specified) were almost 4 times greater with empagliflozin compared with sitagliptin (3.5% vs. 0.7%, RR 3.99; 95% CI 1.08 to 14, I^2=0%, moderate strength of evidence) but there was no difference in risk of a urinary tract infection (8% vs. 6%; RR 1.06, 95% CI 0.64 to 1.77, I^2=0%).

Linagliptin compared with empagliflozin

Two 24-week, fair-quality trials compared empagliflozin 25 mg and empagliflozin 10 mg with linagliptin 5 mg in patients who were either not receiving antidiabetic medication (n=370)[23] or were inadequately controlled on metformin (n=397).[16] Pooling results from both studies and both empagliflozin doses indicated no differences in risk of experiencing any adverse event (73% vs. 71%; RR 1.03, 95% CI 0.94 to 1.13, I^2=0%) or in rates of study withdrawal due to adverse events between empagliflozin and linagliptin (5% vs. 2%; RR 1.99, 95% CI 0.83 to 4.77, I^2=0%). However, genital infections were more likely with empagliflozin treatment than treatment with linagliptin (7% v. 3%; RR 2.50, 95% CI 1.11 to 5.47, I^2=0%) but not urinary tract infections (13% vs. 13%; RR 1.00, 95% CI 0.69 to 1.47, I^2=28%). There was also no difference between treatments in risk of hypoglycemia (2% vs. 2%; RR 1.43, 95% CI 0.47 to 4.36, I^2=0%). No hypoglycemic events requiring assistance were reported in either study.

Saxagliptin compared with dapagliflozin

One trial (n=355) enrolled patients who were poorly controlled on metformin to add-on therapy with saxagliptin 5 mg or dapagliflozin 10 mg.[31] There was low strength evidence that the risk of experiencing any adverse event and withdrawals due to adverse events were similar between dapagliflozin and saxagliptin (49% vs. 53%; RR 0.92, 95% CI 0.75 to 1.13; 0.6% vs. 0%; RR 2.95, 95% CI 0.12 to 72, respectively). There was additional low strength evidence of more genital infections with dapagliflozin than with saxagliptin (6% vs. 0.6%; RR 9.83, 95% CI 1.27 to 76) but not urinary tract infections (5% both groups; RR 0.77, 95% CI 0.29 to 2.01). Hypoglycemic events were experienced by 2 individuals (1%) in each treatment arm but none were considered major (strength of evidence insufficient).

III. Newer Diabetes Medications compared with metformin: Harms

Key Findings: Harms

DPP-4 inhibitors compared with metformin

- Two trials compared linagliptin 5 mg with either metformin 500 mg twice daily or 1,000 mg twice daily. Our meta-analyses showed no difference between linagliptin 5 mg and metformin 1,000 mg twice daily for withdrawals due to adverse events (k=2, RR for withdrawals due to adverse events 1.21, 95% CI, 0.52 to 2.78) (strength of evidence: low) In 1 trial, there were no significant differences between groups for other adverse events at 24 weeks; however, compared with patients receiving linagliptin, patients receiving metformin 1,000 mg twice daily experienced higher rates of hypoglycemia (3.4% vs. 0%; strength of evidence: low). Rates of other adverse events were similar between groups. No cases of pancreatitis occurred during the 24-week treatment period.
- In 1 trial comparing alogliptin 25 mg with metformin 500 mg and 1,000 mg twice daily over 26 weeks, rates of withdrawal due to adverse events were similar across groups. (strength of evidence: low).
- Two trials compared saxagliptin 5 mg to metformin over 18 and 24 weeks.[64,65] Our meta-analyses showed no difference between saxagliptin and metformin for withdrawals due to adverse events (strength of evidence: low). Compared with metformin, saxagliptin was associated with an increased risk of hypoglycemia (k=2, RR 2.93, 95% CI, 1.08 to 7.97; strength of evidence low).

GLP-1 analogs compared with metformin

- Rates of withdrawal due to adverse events were not reported in the single trial comparing exenatide 10 µg twice daily to metformin over 26 weeks. Hypoglycemia was also reported significantly more often in the exenatide arm than in the metformin arm (12% vs. 3.2%, $P<0.05$); episodes of severe hypoglycemia were not reported.
- One trial compared exenatide XR 2 mg weekly to metformin 2,000 mg per day over 26 weeks. Withdrawals due to adverse events occurred at similar rates in the exenatide and metformin arms. Differences between the groups in rates of overall adverse events and hypoglycemia were not statistically significant.
- One trial (n=807) compared dulaglutide 0.75 mg or 1.5 mg to metformin 1,500 mg to 2,000 mg over 26 weeks, with extension to 52 weeks.[36] No differences between groups were reported for overall adverse events or withdrawal due to adverse events, and there were no cases of severe hypoglycemia (strength of evidence: low).

SGLT2 inhibitors compared with metformin

- Three trials described in 2 publications compared dapagliflozin 5 mg and 10 mg with metformin XR daily over 12 and 24 weeks. We did not find any significant differences between dapagliflozin 5 mg and metformin XR in overall adverse events or withdrawal due to adverse events (strength of evidence: low).
- Two trials (n=660 and 336) compared empagliflozin 25 mg and 10 mg with metformin and reported no differences between groups for overall adverse events (77% vs. 77% vs. 86% in 1 study and 63% vs. 69% vs. 70% in the other study for empagliflozin 10 mg,

empagliflozin 25 mg, and metformin, respectively) or withdrawal due to adverse events (2.9% vs. 3.7% vs. 4.8% in 1 study and 4.7% vs. 0.9% vs. 1.8% in the other study); there was a single case of severe hypoglycemia (in a patient receiving metformin) in 1 of the studies, with no severe hypoglycemia reported in the other study (strength of evidence: low).

Overview

For harms outcomes, we included 12 trials (described in 15 publications) from the prior report and 3 newly identified trials comparing a newer diabetes drug with metformin. Of these, 8 compared a DPP-4 inhibitor with metformin: linagliptin (2 trials)[59,69,72], alogliptin (1 trial),[60] sitagliptin (4 trials),[51,61,63,70,71] and saxagliptin (2 trials).[64,65] Three trials compared metformin with a GLP-1 analog.[36,51,66] One trial compared metformin with exenatide over 26 weeks;[66] 1 three-arm trial compared exenatide XR with metformin and sitagliptin[51]; and 1 trial compared with dulaglutide.[36] Six trials compared the SGLT2 inhibitor dapagliflozin with metformin[14,30,40,67,68]; 3 (in 2 publications) assessed dapagliflozin[67,68], two assessed empagliflozin[14,40] and 1 assessed canagliflozin[30]; this last trial also assessed the combination of canagliflozin and metformin. Details of these trials are presented in Table 5 in the corresponding section of Key Question 1 and in the Evidence Tables (included in a separate file).

Detailed Assessment for Newer Diabetes Medications compared with Metformin: Harms

DPP-4 inhibitors compared with metformin

Linagliptin compared with metformin

Two trials (described in 2 published articles and 1 unpublished trial synopsis) compared linagliptin 5 mg with either metformin 500 mg twice daily or 1,000 mg twice daily.[59,69,72] For linagliptin 5 mg compared with metformin 1,000 mg twice daily, our meta-analyses of 2 trials showed no difference for withdrawals due to adverse events (k=2, RR for withdrawals due to adverse events 1.21, 95% CI, 0.52 to 2.78) or diarrhea (k=2, RR for diarrhea 0.54, 95% CI, 0.19 to 1.50). In 1 trial, at 24 weeks the rate of withdrawal due to adverse events was higher in the linagliptin 5 mg arm than in the metformin 500 mg twice daily arm (4.2% compared with 2.1%).[59]

Only 1 of the trials reported rates for other adverse events for linagliptin and both doses of metformin.[59] At 24 weeks, rates of specific adverse events were generally low in all groups. No cases of pancreatitis occurred during the 24 week treatment period.

Alogliptin compared with metformin

In the 1 trial comparing alogliptin 25 mg once daily with metformin 500 mg and 1,000 mg twice daily over 26 weeks, rates of withdrawal due to adverse events were similar, with a slightly higher percentage of patients in the alogliptin 25 mg once daily arm (3.6%) withdrawing because of adverse events than in the 2 metformin monotherapy arms (2.6% in the metformin 500 mg twice daily arm and 1.8% in the metformin 1,000 mg twice daily arm). The frequency of hypoglycemic events were similar with alogliptin 25 mg daily and metformin 500 mg twice daily (1.8% both groups) compared with 6.3% with metformin 1000 mg twice daily but this difference was not statistically significant.. There were no instances of severe hypoglycemia.

Sitagliptin compared with metformin

We included 3 trials (described in 5 publications) for harms that compared sitagliptin with metformin,[51,61,63,70,71] Meta-analysis of these trials found no statistically significant difference between sitagliptin and metformin for overall adverse events, withdrawal due to adverse events, or hypoglycemia.

Saxagliptin compared with uptitrated metformin

Two trials compared saxagliptin 5 mg to metformin over 18 and 24 weeks.[64,65] Compared with metformin, saxagliptin was associated with an increased risk of hypoglycemia (k=2, RR 2.93, 95% CI 1.08 to 7.97); however, no episodes of severe hypoglycemia were reported in either trial. There were no significant differences between saxagliptin and metformin based on pooled estimates for overall adverse events or withdrawals due to adverse events. Results from individual trials are summarized in the Evidence Tables (included in a separate file).

GLP-1 analogs compared with metformin

Exenatide compared with metformin

One trial set in China compared exenatide 10 µg twice daily to metformin over 26 weeks.[66] The rates of withdrawal due to adverse events were not reported. Hypoglycemia was reported significantly more often in the exenatide arm than in the metformin arm (12% compared with 3.2%, $P<0.05$), but severe hypoglycemia was not reported.

Exenatide XR compared with metformin

One trial compared exenatide XR 2 mg weekly to metformin 2,000 mg per day[51] over 26 weeks. Withdrawals due to adverse events occurred at similar rates in the exenatide and metformin arms (2.4% in each group). Differences between the groups in rates of other adverse events were also not statistically significant.

Dulaglutide compared with metformin

One trial (n=807) compared dulaglutide 0.75 mg or 1.5 mg to metformin 1,500 mg to 2,000 mg over 26 weeks, with extension to 52 weeks.[36] No differences between groups were reported for overall adverse events (67% vs. 66% vs. 63%) or withdrawal due to adverse events (5.2% vs. 3.0% vs. 4.5%), and there were no cases of severe hypoglycemia.

SGLT2 inhibitor compared with metformin

Dapagliflozin compared with metformin

Three trials described in 2 publications compared dapagliflozin 5 mg and 10 mg with metformin XR daily over 12 and 24 weeks.[67,68] Results from individual trials are summarized in the Evidence Tables (included in a separate file). We conducted a meta-analysis in the prior report, which found no significant differences between dapagliflozin 5 mg and metformin XR for overall adverse events, withdrawal due to adverse events, or hypoglycemia.

Empagliflozin compared with metformin

Two trials (n=336 and 660) compared empagliflozin 10 mg or 25 mg with metformin.[14,40] One trial was conducted in Japan over 52 weeks,[14] while the other trial was conducted in an international setting over 12 weeks.[40] No differences between groups were reported for overall adverse events (77% vs. 77% vs. 86% in 1 study and 63% vs. 69% vs. 70% in the other study for

empagliflozin 10 mg, empagliflozin 25 mg, and metformin, respectively) or withdrawal due to adverse events (2.9% vs. 3.7% vs. 4.8% in 1 study and 4.7% vs. 0.9% vs. 1.8% in the other study) in either study; there were no cases of severe hypoglycemia reported in either study.

Canagliflozin compared with metformin

One trial (n=1,186) compared canagliflozin 100 mg and 300 mg with metformin over 26 weeks.[30] No differences between groups were reported for overall adverse events (rates ranging from 37% to 44%) or withdrawal due to adverse events (rates ranging from 1.3% to 3.0%), and there were only a single case of severe hypoglycemia (in a patient receiving metformin).

IV. Fixed-dose Combination Products (FDCPs) or Dual Therapy

Key Findings: Harms

- One trial of combination therapy with alogliptin plus pioglitazone compared to component monotherapy found no differences in rates of overall adverse events or withdrawal due to adverse events (strength of evidence: insufficient). No cases of severe hypoglycemia, bone fracture, or congestive heart failure were reported.
- At 26 weeks, rates of withdrawals due to adverse events in 1 trial of Kazano® or dual therapy with alogliptin and metformin ranged from 1.8% in the metformin 1,000 mg twice daily group to 9.6% in the alogliptin 12.5 mg plus metformin 500 mg twice daily group. Hypoglycemia occurred more frequently in the groups receiving the highest doses of metformin (1,000 mg twice daily either as monotherapy or in combination with alogliptin) than in the other groups (strength of evidence: low).
- The rates of withdrawal due to adverse events in two trials of Jentadueto® or dual therapy with linagliptin plus metformin ranged from 1.3% to 4.2%, with no differences between groups, and rates of overall adverse events also did not differ between groups (strength of evidence: low).
- Two trials of Janumet® or dual therapy with sitagliptin and metformin found that incidences of adverse events were generally similar between treatment arms and the rate of withdrawals due to adverse events was low. Hypoglycemic events were rare across treatment groups and none were severe. Our meta-analysis from the prior report for sitagliptin 50 mg plus metformin 100 mg twice daily compared with metformin 1,000 mg twice daily found no difference between groups for hypoglycemia (k=2, pooled RR 1.75, 95% CI, 0.50 to 6.10; strength of evidence: low).
- Two trials (n=686 and 677) compared Glyxambi®/empagliflozin plus linagliptin to component monotherapy and reported no differences in overall adverse events (rates ranging from 68% to 73% in 1 study and from 69% to 82% in the other study), withdrawal due to adverse events (rates ranging from 1.5% to 6.4% in 1 study and from 1.5% to 6.6% in the other), or hypoglycemia (strength of evidence: low).

Overview

We included 3 trials (described in 7 publications) from the previous report and 4 newly identified trials for harms specifically using fixed dose combination products or dual therapy with individual components of fixed dose combination products.[16,23,30,34,59,60,63,70-73] Study characteristics are described under Key Question 1 and in Table 5.

Detailed Assessment for FDCPs and Dual Therapy

Oseni® or dual therapy with alogliptin plus pioglitazone

One trial (n=654) compared dual therapy with alogliptin plus pioglitazone to component monotherapy.[74]Harms were sparsely reported, but the rate of overall adverse events did not differ between the group with the lowest rate (alogliptin 25 mg) and the group with the highest rate (alogliptin 25 mg plus pioglitazone 30 mg) (55% vs. 65%; RR 1.19, 95% CI 0.99 to 1.42). Likewise, rates of withdrawal due to adverse events did not differ between the group with the lowest rate (alogliptin 25 mg) and the group with the highest rate (alogliptin 25 mg plus pioglitazone 30 mg) (1.8% vs. 4.3%; RR 0.43, 95% CI 0.11 to 1.62). There were no cases of congestive heart failure, bone fracture, or severe hypoglycemia.

Kazano® or dual therapy with alogliptin plus metformin

We identified 1 trial of Kazano® or dual therapy with alogliptin and metformin.[60] At 26 weeks, rates of withdrawals due to adverse events in each group ranged from 1.8% in the metformin 1,000 mg twice daily group to 9.6% in the alogliptin 12.5 mg plus metformin 1000 mg group. None of the participants experienced severe hypoglycemia.

Jentadueto® or dual therapy with linagliptin plus metformin

Two trials meeting inclusion criteria compared Jentadueto® or dual therapy with linagliptin plus metformin, linagliptin monotherapy or metformin monotherapy.[34,59] The rates of withdrawal due to adverse events ranged from 1.3% to 4.2%, with no significant differences between groups. Overall adverse events also did not differ between groups.

Janumet® or dual therapy with sitagliptin plus metformin

Two trials of Janumet® or dual therapy with sitagliptin and metformin met our inclusion criteria.[63,70,71,73] One trial resulted in 3 publications; 1 reporting results after 24 weeks,[63] 1 reporting results after 54 weeks,[70] and the other after a total of 104 weeks.[71] Our meta-analyses of 2 trials comparing sitagliptin 50 mg plus metformin 1,000 mg twice daily with metformin 1,000 mg twice daily found no significant differences in overall adverse events or withdrawal due to adverse events.

Incidences of adverse events were generally similar between treatment arms in both trials. Withdrawals due to adverse events were low, ranging from 1.1% to 2.8% during the first 24 weeks and 2% to 4% during the entire study period in 1 trial, and reaching 4% in the other trial at 18 weeks. Hypoglycemic events were rare across treatment groups in both trials at 18, 24, 54, and 104 weeks and were of mild or moderate severity.

Invokamet® or dual therapy with canagliflozin plus metformin

One trial (n=1,186) compared dual therapy with canagliflozin 100 mg or 300 mg plus metformin XR to component monotherapy over 26 weeks.[30] No differences were reported in rates of overall adverse events (rates ranging from 37% to 44%) or withdrawal due to adverse events (rates ranging from 1.3% to 3.0%). Only 1 episode of severe hypoglycemia, which occurred in a patient receiving metformin, was reported in this trial.

Glyxambi® or dual therapy with empagliflozin plus linagliptin

Two trials[16,23] (n=677 and 686) compared dual therapy with empagliflozin plus linagliptin to component monotherapy over 52 weeks (with the primary endpoint at 24 weeks). One study was conducted in drug-naïve patients,[23] while the other was conducted in patients whose diabetes was inadequately controlled on metformin monotherapy.[16] No differences between groups in overall adverse events (rates ranging from 68% to 73% in 1 study and from 69% to 82% in the other study), withdrawal due to adverse events (rates ranging from 1.5% to 6.4% in 1 study and from 1.5% to 6.6% in the other), or hypoglycemia were reported in either trial. Pancreatitis was reported in 1 patient in each trial (1 receiving linagliptin and 1 receiving empagliflozin 25 mg plus linagliptin 5 mg).

Safety Outcomes

There are numerous additional studies, primarily placebo-controlled trials, pooled analyses of placebo-controlled trials, pooled analyses of trials that compare a study drug with all other comparators analyzed together, and observational studies of newer diabetes drugs that do not meet inclusion criteria for this review. Many of these studies address cardiovascular outcomes and indicate cardiovascular protection for some newer diabetes drugs and increased cardiovascular events for others. Some studies indicate neither increase nor decrease in rate of cardiovascular-related harms with included drugs relative to placebo or all other comparators combined.

Key Question 3. Are there subgroups of patients based on demographics (e.g. age, racial groups, gender), comorbidities (e.g., drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) differ in efficacy/effectiveness or tolerability and frequency of adverse events?

Key Findings

- There was no evidence of a difference between treatment with SGLT2 inhibitors and DPP-4 inhibitors on genital infections based on gender.
- One randomized trial (n=1,160) conducted in Japan enrolled patients on various background therapies and compared empagliflozin 10 mg with empagliflozin 25 mg; reductions in HbA1c from baseline varied based on background therapy.
- One randomized trial (n=495) of albiglutide versus sitagliptin in patients (mean age 63 years) with renal impairment (52% mild, 41% moderate, and 7% severe) found greater reduction in HbA1c from baseline with albiglutide (0.83% vs. 0.52%) with similar risk of experiencing any adverse event, withdrawing from the study due to adverse events, and gastrointestinal adverse events. Hypoglycemic events were similar between treatments after controlling for coadministration of a sulfonylurea.

Detailed Assessment

Genital infections and gender

In patients treated with empagliflozin, canagliflozin, and dapagliflozin, the incidence of genital infections was more common than in patients treated with the comparison DPP-4 inhibitor (sitagliptin, linagliptin, and saxagliptin).[16,23,29,40,54,56] Women tend to develop a genital infection

more frequently than men but this difference is more pronounced with SGLT2 inhibitor treatment. In the currently included trials that compared an SGLT2 inhibitor with a DPP-4 inhibitor and reported genital infections by gender, we explored whether there were significant effects based on gender when comparing the two classes of drugs. Results are in Table 7. For every drug comparison, confidence intervals for men and women overlap. Confidence intervals also overlap when pooling all trials of SGLT2 inhibitors versus all trials of DPP-4 inhibitors indicating that the treatment comparison between SGLT2 inhibitors and DPP-4 inhibitors is not different based on gender.

Table 7. SGLT2 inhibitors versus DPP-4 inhibitors in risk of genital infection by gender

	Empagliflozin	Sitagliptin	Relative Risk (95% CI)
Males	5/171 + 6/286 = 11/457 = 2%	0/29 + 1/141 = 1/170 = 1%	RR 2.55 (0.47, 14)
Females	6/161 + 10/161 = 16/322 = 5%	0/27 + 1/82 = 1/109 = 1%	RR 3.98 (0.78, 20)
M vs F	RR 0.48 (0.23, 1.01)	RR 0.58 (0.04, 9.17) 1 trial	
	Canagliflozin	**Sitagliptin**	
Males	19/207 + 13/399 = 32/606 = 5%	1/215 + 2/172 = 3/387 = 1%	RR 7.20 (2.40, 22)
Females	26/170 + 42/396 = 68/566 = 12%	7/163 + 5/194 = 12/357 = 3%	RR 3.83 (2.08, 7.04)
M vs F	RR 0.43 (0.28, 0.64)	RR 0.24 (0.07, 0.80)	
	Empagliflozin	**Linagliptin**	
Males	8/155 + 3/141 = 11/296 = 4%	2/64 + 1/75 = 3/139 = 2%	RR 1.63 (0.46, 5.80)
Females	15/134 + 10/124 = 25/258 = 10%	1/64 + 3/58 = 4/122 = 3%	RR 2.95 (1.05, 8.30)
M vs F	RR 0.38 (0.19, 0.76)	RR 0.66 (0.16, 2.76)	
	All SGLT2 inhibitors	**ALL DPP-4 inhibitors**	
Males	54/1359 = 4%	7/696 = 1%	RR 3.91 (1.92, 7.99, i2=0%)
Females	109/1146 = 10%	17/588 = 3%	RR 3.62 (2.20, 5.97, I2=0%)

Abbreviations: M vs F, males versus females; RR, relative risk

Effectiveness of empagliflozin based on background treatment

One fair-quality randomized trial (n=1,158) enrolled Japanese patients on background therapy for diabetes and compared treatment with empagliflozin 25 mg and empagliflozin 10 mg.[14] Background therapy included biguanide, thiazolidinediones TZD), α-glucosidase inhibitors (AGI), DPP-4 inhibitors and Glinides. In patients treated with empagliflozin 25 mg, compared with AGI background therapy, changes from baseline in HbA1c at 52 weeks were greater with background biguanide, TZDs, DPP-4 inhibitors and glinides and were best with biguanide, glinide, and TZDs (Table 8). In patients treated with the lower dose empagliflozin, HbA1c values were improved more with background DPP-4 inhibitors followed by glinides.

Table 8. Empagliflozin treatment against background therapy in lowering of HbA1c

Background therapy	Biguanide n=68	n=65	TZD n=137	n=136	AGI n=69	n=70	DPP-4 inhibitor n=68	n=71	Glinide n=70	n=70
Empagliflozin	**10 mg**	**25 mg**	**10 mg**	**25 mg**	**10 mg**	**25 mg**	**10 mg**	**25 mg**	**10 mg**	**25 mg**
					HbA1c					
Baseline	7.68 ± 0.09	7.51 ± 0.09	7.85 ± 0.06	7.95 ± 0.07	7.78 ± 0.10	7.56 ± 0.07	7.78 ± 0.08	7.82 ± 0.09	8.01 ± 0.10	7.98 ± 0.10
Change	−0.81 ± 0.06	−0.98 ± 0.06	−0.90 ± 0.05	−0.96 ± 0.05	−0.87 ± 0.06	−0.77 ± 0.06	−1.00 ± 0.06	−0.83 ± 0.06	−0.98 ± 0.08	−0.98 ± 0.08
***P* value vs DPP-4**	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	---	---	*P*=0.100	*P*<0.001
***P* value vs.**	---	---	*P*<0.001	*P*=0.014	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001

Background therapy	Biguanide n=68	n=65	TZD n=137	n=136	AGI n=69	n=70	DPP-4 inhibitor n=68	n=71	Glinide n=70	n=70
Empagliflozin	**10 mg**	**25 mg**	**10 mg**	**25 mg**	**10 mg**	**25 mg**	**10 mg**	**25 mg**	**10 mg**	**25 mg**
					HbA1c					
biguanide										
***P* value vs. TZD**	---	---	---	---	*P*<0.001	*P*<0.001	---	---	*P*<0.001	*P*=0.029
***P* value vs. AGI**	---	---	---	---	---	---	---	---	*P*<0.001	*P*<0.001

Albiglutide compared with sitagliptin

One fair quality randomized trial (n=495) of albiglutide versus sitagliptin in patients (mean age 63 years) with renal impairment (52% mild, 41% moderate, and 7% severe) reported greater reduction in HbA1c from baseline with albiglutide (0.83% vs. 0.52%) with similar risk of experiencing any adverse event (84% vs. 83%; RR 1.00, 95% CI 0.93 to 1.08), withdrawing from the study due to adverse events (10% vs. 10%; RR 0.99, 95% CI 0.59 to 1.65), and gastrointestinal adverse events (32% vs. 25%; RR 1.26, 95% CI 0.95 to 1.67).[22] Hypoglycemic events were similar between treatments after controlling for coadministration of a sulfonylurea (2% vs. 2%; RR 0.99, 95% CI 0.25 to 3.91). These results were similar to a trial of albiglutide compared with sitagliptin discussed under key questions 1 and 2.[13] Subgroup analysis from this second trial indicated no differences in effect estimates of albiglutide versus sitagliptin based on baseline HbA1c, age, baseline BMI, or duration of diabetes.

SUMMARY

Strength of Evidence

We identified 52 studies including 43 trials (22 this update) and 5 companion publications (4 this update), 3 observational studies (all this update), and 1 systematic review (this update). All trials enrolled adults with type 2 diabetes mellitus and evaluated intermediate outcomes such as changes in HbA1c and weight. Long-term health outcomes (e.g., death, myocardial infarction, cerebral vascular accident) were incidentally reported in trials and were rare enough that no meaningful conclusions could be drawn from the evidence. We also had few observational studies of harms that met inclusion criteria.

Ten trials compared two medications of the same class. There was moderate-strength evidence that exenatide XR reduced HbA1c from baseline more than exenatide. There was low-strength evidence that liraglutide and dulaglutide decreased HbA1c more than exenatide. Albiglutide and higher-dose dulaglutide reduced weight more than exenatide. However, there was greater weight loss with liraglutide than either albiglutide or dulaglutide, and liraglutide was also associated with a greater proportion of patients achieving an HbA1c <7% than albiglutide.

There were 17 trials that compared 1 drug class with another; all comparisons were made against a DPP-4 inhibitor. The 9 trials that compared a GLP-1 analog with a DPP-4 inhibitor provided low-strength evidence that exenatide XR, albiglutide, and liraglutide reduced HbA1c values from baseline greater than sitagliptin. Exenatide XR, dulaglutide, and liraglutide also were associated with increased weight loss compared with sitagliptin. Treatment with liraglutide reduced HbA1c and resulted in greater weight loss than treatment with saxagliptin. However, there was low-strength evidence that gastrointestinal adverse events were lower with sitagliptin

than with exenatide XR, liraglutide, albiglutide and dulaglutide. Gastrointestinal adverse events were also lower with saxagliptin than with liraglutide.

The 8 trials that compared a SGLT2 inhibitor with a DPP-inhibitor provided moderate-strength evidence that treatment with canagliflozin decreased HbA1c and increased weight loss from baseline compared with sitagliptin. Empagliflozin treatment was also associated with greater weight loss than with sitagliptin or linagliptin based on moderate-strength evidence. Additionally, there was moderate-strength evidence that empagliflozin treatment resulted in decreased HbA1c and increased proportions of patients achieving an HbA1c < 7% compared with linagliptin. There was low-strength evidence that dapagliflozin was associated with greater weight loss than saxagliptin and that sitagliptin treatment resulted in greater numbers with <7% HbA1c at study's end than with canagliflozin 100 mg. However, treatment with sitagliptin resulted in lower rates of genital infections than treatment with canagliflozin and empagliflozin based on low-strength evidence. Rates of genital infections were also lower with saxagliptin compared with dapagliflozin and with linagliptin compared with empagliflozin.

Twelve studies compared a newer diabetes drug with metformin. There was moderate-strength of evidence that treatment with metformin improved HbA1c values more than linagliptin, alogliptin, and sitagliptin but less improvement was found with metformin than with dulaglutide (low-strength evidence). There was also low-strength evidence of greater weight loss with metformin than with sitagliptin, alogliptin, dulaglutide and linagliptin but metformin was associated with less weight loss when compared with canagliflozin, dapagliflozin, and empagliflozin. Treatment with metformin was also associated with greater gastrointestinal adverse events than was sitagliptin and alogliptin.

Five trials compared either a fixed-dose combination product or dual therapy with component monotherapy. There was low- to moderate-strength of evidence that dual therapy with alogliptin, linagliptin, sitagliptin, canagliflozin and empagliflozin in combination with metformin, as well as alogliptin in combination with pioglitazone, reduced HbA1c values more than component monotherapy. Weight loss in combination therapy with metformin was also improved compared with alogliptin or canagliflozin treatment alone. However, there was low-strength evidence that both the combination of alogliptin and metformin therapy, and metformin therapy alone were associated with more frequent gastrointestinal adverse events versus alogliptin alone.

Limitations of this Report

Methodological limitations of the review within the defined scope included the exclusion of trials published in languages other than English. For this streamlined update, our scope was also limited to head-to-head trials of included drugs and comparisons with metformin only. There were also no between class comparisons of a GLP-1 analog with a SGLT2 inhibitor. Most between-class trials used sitagliptin as the active comparator. In addition, there were no trials of alogliptin compared with a GLP-1 analog or a SGLT2 inhibitor or of the combination product empagliflozin with linagliptin. Finally, the data from some randomized controlled trials included in this report have limited utility for assessing real-world adherence to medications. This is largely because they enrolled selected populations, often requiring adherence during a run-in period before randomization.

Applicability

Most trials represented a selected population: primarily white, middle-aged, obese adults with moderately elevated baseline HbA1c (<9%) and diabetes for less than 10 years. It is unclear if the reductions in HbA1c found in the included trials would be consistent with what is expected in general practice. Many trials included narrowly defined populations of patients who had to undergo placebo run-in periods prior to randomization. Minorities and patients with comorbidities were generally underrepresented.

Table 9. Summary of evidence by Key Question

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?
Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?

Strength of evidence[a]	Conclusions
Within Class Comparisons: Saxagliptin vs. Sitagliptin	
Low	Two trials (n=801 and 139) found no difference between sitagliptin and saxagliptin for reducing HbA1c or in the proportion of patients achieving an HbA1c <7% over 18 and 24 weeks.
Insufficient	Evidence was insufficient to determine the comparative efficacy of sitagliptin and saxagliptin for reducing weight.
Moderate	Rates of adverse events were similar between groups over 18 or 24 weeks.
Low	Rates of withdrawals due to adverse events were similar between groups over 18 or 24 weeks.
Within Class Comparisons: Exenatide XR vs. Exenatide	
Insufficient	Two trials (n=547) found no difference between exenatide XR and exenatide for improving cardiovascular events. One trial measured “myocardial infarction” and the other “fatal myocardial infarction.” (1 trial for each measurement; unknown consistency; imprecise findings).
Moderate	We pooled data from 3 trials (n=1,225) comparing exenatide XR with exenatide administered twice daily over 24 to 30 weeks. Exenatide XR was more efficacious in reducing mean HbA1c than exenatide twice daily: WMD −0.46% (95% CI −0.69 to −0.23).
Low	Three trials found no difference between exenatide XR and exenatide administered twice daily for weight changes over 24 to 30 weeks; 2 trials found no difference between groups and 1 trial found a small reduction in weight (−0.33 kg; *P*<0.001) favoring exenatide twice daily.
Low	There was no difference between groups for rates of withdrawals because of adverse events (3 trials, n=1,223, RR 0.72, 95% CI 0.35 to 1.50).
Within Class Comparisons: Exenatide vs. Liraglutide	
Low	In 1 trial (n=464), liraglutide 1.8 mg once daily reduced mean HbA1c more than exenatide 10 µg twice daily (between-group difference: −0.33%, 95% CI −0.47 to −0.18).
Insufficient	One trial (n=464) found no difference between exenatide and liraglutide 1.8mg for weight changes. Both drugs were associated with weight loss.
Low	In 1 trial, rates of withdrawal due to adverse events were similar between groups over 26 weeks.
Within Class Comparisons: Exenatide vs. Dulaglutide	

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?
Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?

Strength of evidence[a]	Conclusions
Low	One trial (n=976) compared exenatide with dulaglutide and reported that rates of achieving HbA1c <7% were significantly higher for dulaglutide 1.5 mg (78%) and 0.75 mg (66%) than exenatide (52%) (all *P*<0.001). Similarly, mean change in HbA1c was also significantly greater in patients receiving dulaglutide than those receiving exenatide (*P*<0.001).
Low	One trial (n=976) compared exenatide with dulaglutide, reporting no differences between groups were reported for overall adverse events.
Insufficient	One trial (n=976) compared exenatide with dulaglutide, reporting no differences between groups were reported for withdrawal due to adverse events, or specific adverse events.
Within Class Comparisons: Exenatide vs. Albiglutide	
Insufficient	One trial (n=66) reported no difference between groups in weight loss.
Insufficient	Evidence for HbA1c was insufficient.
Insufficient	One trial (n=66) compared albiglutide with exenatide, reporting no differences between groups were reported for overall adverse events, withdrawal due to adverse events, or specific adverse events.
Within Class Comparisons: Dulaglutide vs. Liraglutide	
Low	One trial (n=599) of dulaglutide compared with liraglutide found no differences in mean reduction in HbA1c or the proportion of patients achieving an HbA1c <7% (RR 1.01, 95% CI 0.90 to 1.12).
Low	Body weight was significantly reduced with liraglutide (treatment difference: 0.71 kg).
Low	No difference in rates of gastrointestinal events (36% vs. 36%; RR 1.00, 95% CI 0.81 to 1.24).
Insufficient	One trial (n=599) compared dulaglutide with liraglutide, reporting no differences between groups were reported for overall adverse events or withdrawal due to adverse events.
Within Class Comparisons: Albiglutide vs. Liraglutide	
Low	One trial (n=841) of albiglutide compared with liraglutide found that mean HbA1c reduction and the proportion of patients achieving HbA1c <7% was significantly greater with liraglutide (RR 1.23, 95% CI 1.06 to 1.42).
Low	Liraglutide was also associated with significantly more weight loss (treatment difference: 1.55 kg, 95% CI 1.05 kg to 2.06 kg).
Low	One trial (n=841) compared albiglutide to liraglutide, reporting no differences between groups were reported for overall adverse events.
Insufficient	One trial (n=841) compared albiglutide to liraglutide, reporting no differences between groups were reported for withdrawal due to adverse events.
Between Class Comparisons: Exenatide XR vs. Sitagliptin	
Low	Two trials (n=753) indicated greater reduction in HbA1c and greater proportions of patients achieving a HbA1c < 7% with exenatide XR compared with sitagliptin 100 mg (62% vs. 39%, RR 1.57, 95% CI 1.34 to 1.83)
Low	Exenatide XR treatment resulted in greater reduction in weight loss compared with sitagliptin (WMD −1.32, 95% CI −1.87 to −0.76)

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Strength of evidence[a]	Conclusions
Low	Increased withdrawals due to adverse events found with exenatide XR vs. sitagliptin (RR 2.61, 95% CI 1.03 to 6.61)
Low	Nausea (RR 2.62, 95% CI 1.66 to 4.15), vomiting (RR 3.67, 95% CI 1.63 to 8.24) and diarrhea (RR 1.91, 95% CI 1.22 to 3.00) increased with exenatide compared with sitagliptin
Between Class Comparisons: Liraglutide vs. Sitagliptin	
Low	One trial (n=665) found increased proportions of patients achieving a HbA1c <7% with liraglutide at both dosages (1.2 mg and 1.8 mg) compared with sitagliptin 100 mg once daily (liraglutide 1.2 mg: OR 2.75, 95% CI 1.78 to 4.25; liraglutide 1.8 mg OR 4.50, 95% CI 2.90 to 6.97) at 26 weeks. At 52 weeks: OR 2.80 (95% CI 1.74 to 4.48) for liraglutide 1.2 vs. sitagliptin; OR 4.37 (95% CI 2.74 to 6.98) for liraglutide 1.8
Low	One trial (n=665) found liraglutide at both dosages (1.2 mg and 1.8 mg) to be more efficacious than sitagliptin 100 mg once daily in reducing weight at 26 and 52 weeks. Change in weight at 26 weeks: liraglutide 1.2 mg −2.86 kg, liraglutide 1.8 mg −3.38 kg; sitagliptin −0.96 kg; *P*<0.001 for both comparisons. Weight loss at 52 weeks −2.78 kg (liraglutide 1.2 mg), −1.8 (liraglutide 1.8 mg), −1.16 kg (sitagliptin), *P*<0.001; second trial (n=547) found similar results (liraglutide lowered weight by an average of 2.3 kg, 95% CI 1.8 to 2.9 more than treatment with sitagliptin)
Low	Gastrointestinal adverse events were more likely with liraglutide (RR 1.75, 95% CI 1.31 to 2.32)
Between Class Comparisons: Albiglutide vs. Sitagliptin	
Low	HbA1c was lowered more with albiglutide compared with sitagliptin at 104 weeks (0.63% vs. 0.28%, *P*<0.001) but there was no difference in proportion of patients achieving HbA1c <7% based on 1 trial (n=604)
Low	There were no differences between groups in weight loss at 24 weeks or 104 weeks from baseline.
Low	There were no differences between groups in withdrawal due to adverse events, having one or more adverse events, or having hypoglycemic event
Low	Diarrhea and nausea were more common with albiglutide (RR 1.64, 95% CI 1.06 to 2.56; RR 1.68, 95% CI 1.03 to 2.78)
Between Class Comparisons: Dulaglutide vs. Sitagliptin	
Low	Achieving HbA1c <7% was more likely with dulaglutide 0.75 mg and 1.5 mg compared with sitagliptin 100 mg at 26 weeks (n=230; 55% and 61% vs. 38%, *P*<0.001 for both comparisons) and at 104 weeks (n=1,098; RR 1.44, 95% CI 1.17 to 1.77; RR 1.75, 95% CI 1.44 to 2.12) based on one adaptive trial with a second randomization at 26 weeks.
Low	At 26 weeks weight loss was greater for both doses of dulaglutide compared with sitagliptin (*P*<0.001 for both comparisons) but at 104 weeks only dulaglutide 1.5 mg was associated with greater weight loss (*P*<0.05)
Low	There were no differences between dulaglutide and sitagliptin in withdrawal due to adverse events or in hypoglycemic events.
Low	Gastrointestinal events were more likely with dulaglutide at both 26 weeks (RR 1.84, 95% CI 1.38 to

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Strength of evidence[a]	Conclusions
	2.46) and at 104 weeks (RR 1.44, 95% CI 1.19 to 1.74)
Between Class Comparisons: Liraglutide vs. Saxagliptin	
Low	There were no differences between treatment with liraglutide and saxagliptin in change in HbA1c levels based on 1 trial (n=121)
Low	Liraglutide resulted in greater weight loss compared with saxagliptin (−6 kg, 95% CI −6.8 to −5.3 vs. −0.9 kg, 95% CI −1.5 to −0.4)
Low	There were no differences between groups in study withdrawals due to adverse events and in hypoglycemic events.
Low	Liraglutide was associated with increased risk of experiencing any adverse event (RR 2.46, 95% CI 1.43 to 4.23) and nausea (RR 8.37, 95% CI 2.02 to 35)
Between Class Comparisons: Canagliflozin vs. Sitagliptin	
Moderate	There was moderate strength evidence based on a good quality systematic review (n=1,575) that canagliflozin 300 mg improved HbA1c values at 52 weeks by 0.24% (95% CI −0.40 to −0.09) versus sitagliptin. More patients also achieved HbA1c values < 7% at 52 weeks (RR 1.20, 95% CI 1.07 to 1.33)
Low	There was low strength evidence that treatment with canagliflozin 100 mg was less effective than sitagliptin at achieving a HbA1c <7% (RR 0.66, 95% CI 0.48 to 0.91) based on 1 trial (n=734)
Moderate	Treatment with canagliflozin was associated with greater weight loss than sitagliptin by 2.84 kg (95% CI 2.48 to 3.21)
Low	There were no differences between canagliflozin 300 mg and sitagliptin in study withdrawal due to adverse events, having one or more adverse events or having hypoglycemic events
Moderate	Genital mycotic infections were 4 times more likely with canagliflozin 300 mg than with sitagliptin (RR 4.20, 95% CI 2.51 to 7.03)
Between Class Comparisons: Empagliflozin vs. Sitagliptin	
Moderate	There were no differences between treatment with empagliflozin 25 mg and sitagliptin in achieving a HbA1c <7% based on 2 trials (n=1,003; RR 1.17, 95% CI 0.96 to 1.43); results were similar when treated with empagliflozin 10 mg (RR 0.88, 95% CI 0.70 to 1.10)
Moderate	Weight loss was greater with empagliflozin 25 mg (2.48 kg to 4.30 kg) and empagliflozin 10 mg (2.26 kg to 3.1 kg) compared with sitagliptin (0.4 kg loss to 0.18 kg gain), *P*<0.05 for all comparisons with sitagliptin
Moderate	There was moderate strength evidence of no difference between empagliflozin and sitagliptin in withdrawal due to adverse events (RR 0.77, 95% CI 0.31 to 1.90), having 1 or more adverse events (RR 1.06, 95% CI 0.95 to 1.19)
Low	There was no difference between empagliflozin and sitagliptin in hypoglycemic events based on 1 trial (n=388)
Moderate	Genital infections were more common with empagliflozin treatment than with sitagliptin (RR 3.99, 95%

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Strength of evidence[a]	Conclusions
	CI 1.08 to 14)
Between Class Comparisons: Empagliflozin vs. Linagliptin	
Moderate	There was moderate strength evidence based on 2 trials (n=767) that treatment with empagliflozin 25 mg increased the proportion of participants achieving HbA1c <7% at 24 weeks (OR 3.3, 95% CI 1.9 to 4.6) compared with linagliptin; results were similar with empagliflozin 10 mg (OR 3.3, 95% CI 1.9 to 4.7)
Moderate	Weight loss also favored empagliflozin 25 mg (2.0 kg to 3.0 kg) and empagliflozin 10 mg (2.6 kg to 2.7 kg) compared with linagliptin (0.7 kg to 0.8 kg), *P*<0.01 for comparisons with linagliptin
Moderate	There was moderate strength evidence of no difference between empagliflozin and linagliptin in withdrawal due to adverse events (RR 1.99, 95% CI 0.83 to 4.77), risk of having any adverse event (RR 1.03, 95% CI 0.94 to 1.13) or risk of hypoglycemic (RR 1.43, 95% CI 0.47 to 4.36)
Moderate	Genital infections were more likely with empagliflozin than with linagliptin (RR 2.50, 95% CI 1.11 to 5.47)
Between Class Comparisons: Dapagliflozin vs. Saxagliptin	
Low	There was no difference between dapagliflozin and saxagliptin at 24 weeks in lowering of HbA1c based on 1 trial (n=355)
Low	Weight loss at 24 weeks was greater with dapagliflozin (2.4 kg, 95% CI 1.9 to 2.9) compared with saxagliptin (0 kg, 95% CI 0.5 kg weight loss to 0.5 kg weight gain)
Low	There were no differences between treatments in study withdrawals due to adverse events or risk of experiencing any adverse event
Low	Genital infections were more common with dapagliflozin than with saxagliptin (RR 9.83, 95% CI 1.27 to 76)
Insufficient	Evidence for hypoglycemic events was insufficient to draw conclusions
Newer Diabetes Medications compared with Metformin: Alogliptin vs. Metformin	
Insufficient	One trial (n=338) found no difference between alogliptin and metformin (at either dose) for improving the following health outcomes: mortality, ischemic stroke, heart failure related events, and myocardial infarction (1 trial; unknown consistency; imprecise findings).
Low	One trial (n=338) found no difference between alogliptin 12.5 mg and metformin 500 mg at 26 weeks (0.09%, 95% CI −0.17 to 0.35).
Moderate	One trial (n=338) found a greater reduction in HbA1c with metformin 1,000 mg than alogliptin 12.5 mg twice daily (between-group difference −0.55, 95% CI −0.29 to −0.81).
Low	One trial (n=338) found a greater reduction in weight with metformin 500 mg than alogliptin 12.5 mg twice daily (−0.79 kg, 95% CI −0.003 to −1.58) and metformin 1000 mg twice daily compared with alogliptin 12.5 mg twice daily (−1.4 kg, 95% CI −2.02 to −0.45).
Low	Metformin 1,000 mg twice daily was associated with higher rates of diarrhea, and nausea than the metformin 500 mg twice daily and alogliptin 25 mg once daily groups.

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Strength of evidence[a]	Conclusions
Newer Diabetes Medications compared with Metformin: Sitagliptin vs. Metformin	
Low	Three trials reported mortality over 24 to 26 weeks; there was no difference between groups.
Moderate	Our meta-analysis (3 trials; n=1,655) found that metformin 2,000 mg per day was more efficacious for reducing HbA1c than sitagliptin 100 mg daily (WMD −0.30%, 95% CI −0.52 to −0.09, I^2=84.7%); all trials found a statistically significant benefit favoring metformin; 1 trial found a smaller magnitude of effect (−0.14%) than the other 2 trials (−0.33% and −0.47%).
Low	Metformin was associated with a greater reduction in weight compared with sitagliptin over 24 to 54 weeks (2 trials). Mean difference between groups ranged from −1.2 kg to −1.7 kg.
Low	Compared with metformin monotherapy, sitagliptin was associated with lower incidence of nausea and diarrhea (n=3, RR for nausea 0.45, 95% CI 0.24 to 0.84; n=3, RR for diarrhea 0.35, 95% CI, 0.24 to 0.51).
Newer Diabetes Medications compared with Metformin: Saxagliptin vs. Uptitrated Metformin	
Insufficient	One trial (n=286) found no difference in mortality between the addition of saxagliptin and uptitration of metformin in patients not at goal on submaximal metformin (over 24 weeks); a second trial (n=282) found no difference between saxagliptin and uptitration of metformin for improving cardiovascular events (myocardial infarction and myocardial ischemia).
Low	Our meta-analysis (2 trials; n=1,677) found no difference in HbA1c with the addition of saxagliptin 5 mg compared with uptitration of metformin in patients not at goal on submaximal doses of metformin (WMD −0.31, 95% CI −0.74 to 0.13) (low strength of evidence). Two trials found inconsistent results. One trial found greater reduction in HbA1c with the addition of saxagliptin 5 mg compared with uptitration of metformin (between-group difference: −0.53, 95% CI −0.74 to −0.32). A second trial and another trial found no difference in the change from baseline (between-group difference −0.09%, 95% CI −0.26 to 0.08).
Low	In 1 trial (n=282), the uptitration of metformin was associated with a greater reduction in weight compared with adding saxagliptin 5 mg (between-group difference −0.9 kg, 95% CI −0.24 kg to −1.56 kg).
Low	Compared with metformin, saxagliptin was associated with an increased risk of hypoglycemia (n=2, RR 2.93, 95% CI 1.08 to 7.97), but no differences between groups were found with our meta-analyses for nausea, vomiting, diarrhea, or urinary tract infections.
Newer Diabetes Medications compared with Metformin: Exenatide twice daily vs. Metformin	
Insufficient	One trial (n=59) found greater reduction in HbA1c with exenatide twice daily compared with metformin: −2.6% vs. −1.6%; *P*<0.045 (1 trial; unknown consistency).
Insufficient	One trial found greater reduction in weight with exenatide (−5.8 kg) compared with metformin (−3.81 kg) over 26 weeks, *P*<0.01 (1 trial; unknown consistency).
Newer Diabetes Medications compared with Metformin: Exenatide XR vs. Metformin	
Insufficient	One trial (n=494) found no difference in mortality between exenatide XR and metformin over 24 weeks (1 trial; unknown consistency; imprecise findings).
Low	One trial (n=494) found no difference for reducing HbA1c between exenatide XR and metformin: −1.53% vs.−1.48%, *P*=0.62.

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Strength of evidence[a]	**Conclusions**
Low	One trial (n=494) found no difference in weight reduction between exenatide XR and metformin; both groups lost an average of 2 kg over 24 weeks.
Newer Diabetes Medications compared with Metformin: Dulaglutide vs. Metformin	
Low	One trial (n=807) of dulaglutide compared with metformin found greater mean reduction in HbA1c and proportion of patients achieving HbA1c <7% with dulaglutide than metformin (RR 1.16, 95% CI 1.01 to 1.34)
Low	Weight change was less with dulaglutide 0.75 mg than metformin, while there was no difference in weight change between dulaglutide 1.5 mg and metformin.
Low	No differences between groups were reported for overall adverse events or withdrawal due to adverse events, and there were no cases of severe hypoglycemia.
Newer Diabetes Medications Compared with Metformin: Dapagliflozin vs. Metformin	
Low	Three trials found no difference in mortality rates between groups receiving metformin XR 1,500 mg-2,000 mg daily and dapagliflozin.
Low	We pooled 2 trials (n=522) in a meta-analysis; there was no difference between dapagliflozin 5 mg compared with metformin XR 1500 mg-2000 mg daily (WMD −0.12, 95% CI −0.16 to −0.08). For dapagliflozin 10 mg compared with metformin XR 1,500 mg-2,000 mg daily there was a statistically significant reduction in HbA1c favoring dapagliflozin but the overall magnitude of effect was small and not within a range considered clinically significant (WMD −0.11%, 95% CI −0.11 to −0.05).
Low	Dapagliflozin (at both dosages) is associated with greater weight reduction than metformin XR 1,500 mg-2,000 mg over 24 weeks. Our meta-analysis (2 trials; n=522) found a greater reduction with dapagliflozin 5 mg compared with metformin XR 1,500 mg-2,000 mg daily (WMD −1.18 kg, 95% CI −1.86 to −0.26); similarly, across 2 trials (n=505) a greater reduction in weight was seen with dapagliflozin 10 mg compared with metformin XR 1,500 mg-2,000mg (WMD −1.3kg, 95% CI −1.8 to −0.7).
Moderate	Our meta-analyses showed a significant difference in favor of dapagliflozin in the rate of diarrhea between dapagliflozin 10 mg and metformin XR (n=2, RR 0.26, 95% CI 0.12 to 0.60).
Low	Meta-analyses showed no significant differences between dapagliflozin 5 mg and metformin XR for any of the outcomes for which we conducted meta-analysis (withdrawals because of adverse events, hypoglycemia, nausea, diarrhea, and urinary tract infection)
Newer Diabetes Medications Compared with Metformin: Empagliflozin vs. Metformin	
Low	Two trials (n=660 and 336) of empagliflozin compared with metformin found no differences in mean reduction in HbA1c or the proportion of patients achieving HbA1c <7%.
Low	Weight was reduced more with empagliflozin over 52 weeks, while no difference in weight reduction was observed in the shorter (12-week) study
Low	No differences in overall adverse events or withdrawal due to adverse events.
Newer Diabetes Medications Compared with Metformin: Canagliflozin vs. Metformin	

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Strength of evidence[a]	Conclusions
Low	One trial (n=1,186) of canagliflozin compared with metformin found no differences in mean HbA1c reduction or in the proportion of patients achieving HbA1c <7%.
Low	Weight reduction was greater with canagliflozin 100 mg (−3.0 kg; treatment difference −0.9 kg, 95% CI −1.6 to −0.2 kg) and 300 mg (−3.9 kg; treatment difference −1.8 kg, 95% CI −2.6 to −1.1 kg) compared to metformin (−2.1 kg).
Low	No differences in overall adverse events or withdrawal due to adverse events.
Fixed–dose combination products or dual-therapy; Oseni® or dual therapy with alogliptin plus pioglitazone	
Low	One trial (n=654) found greater mean reduction with dual therapy (–1.56% to –1.71% for dual therapy vs. –0.96% and –1.15% for component monotherapy (p<0.05), and greater proportion achieving HbA1c <7% (53%-63% vs. 24%-34%; RRs ranging from 1.58, 95% CI 1.22 to 2.05 to 2.58, 95% CI 1.92 to 3.46)
Low	Weight gain with higher-dose combination therapy compared to with component monotherapy (3.14 kg vs. –0.29 kg with alogliptin and 2.19 kg with pioglitazone; p<0.05 for both)
Insufficient	No difference between the group with the most events and the group with the least events (RR 1.19, 95% CI 0.99 to 1.42; other data NR)
Insufficient	No difference between the group with the most events and the group with the least events (RR 0.43, 95% CI 0.11 to 1.62; other data NR)
Fixed–dose combination products or dual-therapy; Kazano® or dual therapy with alogliptin plus metformin	
Low	One trial (n=784) compared 2 doses of Kazano® (12.5/500 mg twice daily and 12.5/1,000 mg twice daily) to various doses of its component monotherapies. Both Kazano® 12.5/500 mg twice daily and 12.5/1,000 mg twice daily were more efficacious than component monotherapies in reducing mean HbA1c over 26 weeks. Mean HbA1c change from baseline HbA1c changes from baseline were −1.22% (0.094) and −1.55% (0.090) with 12.5/500 mg and 12.5/1,000 mg twice daily combination therapies, respectively, versus −0.56% (0.093) with alogliptin 12.5 mg twice daily, and −0.65% (0.094) and −1.11% (0.092) with metformin 500 mg and 1,000 mg twice daily monotherapies (*P*<0.001 for all comparisons of combination therapy vs. component monotherapies).
Low	Kazano® 12.5/1,000 mg twice daily resulted in greater weight loss than treatment with alogliptin 12.5 mg twice daily alone (−1.17 kg vs. −0.01 kg *P*=0.003). No difference in weight was found between the remaining comparators: alogliptin 25 mg daily: 0.13 kg, metformin 500 mg twice daily: −0.80 kg, metformin 1,000 mg twice daily: −1.25 kg, Kazano® 12.5/500 mg twice daily: −0.57 kg.
Low	Those receiving metformin 1,000 mg either as monotherapy or in combination with alogliptin had higher rates of hypoglycemia, nausea, and diarrhea compared with those receiving alogliptin 25 mg monotherapy or lower doses of metformin.
Fixed-dose combination products or dual-therapy: Jentadueto® or dual therapy with linagliptin plus metformin	
Moderate	Two trials (n=287 and 316) found greater reduction in HbA1c with linagliptin plus metformin dual therapy than with component monotherapy over 24 weeks (–0.70%, 95% CI –0.98% to –0.42% for 1,000 mg metformin and –1.10%, 95% CI –1.38% to –0.82% for 2,000 mg metformin in one study and −0.8%, 95% CI −1.1% to −0.5% for 1,500-2,000 mg metformin in the other); results were similar compared to metformin monotherapy.

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Strength of evidence[a]	Conclusions
Low	Linagliptin 5 mg plus metformin 1,000-2,000 mg daily was not associated with differences in weight change compared to linagliptin monotherapy in one study (–0.30 kg, 95% CI –0.89 to 0.29), while significantly more weight reduction was observed with combination therapy in the other study (treatment difference −1.31 kg, 95% CI −2.18 kg to −0.44 kg). The group receiving linagliptin 5 mg daily plus metformin 1,000 mg had a small but statistically significant weight gain compared to patients receiving metformin 1,000 mg daily (0.60 kg, 95% CI 0.01 to 1.19). No other groups experienced a significant change in weight.
Low	The rates of withdrawal due to adverse events in two trials of Jentadueto® or dual therapy with linagliptin plus metformin ranged from 1.3% to 4.2%, with no differences between groups, and rates of overall adverse events also did not differ between groups.
Fixed-dose combination products or dual-therapy: Janumet® or dual therapy with sitagliptin plus metformin	
Moderate	Two trials assessed an FDCP or dual therapy with sitagliptin plus metformin. One compared dual therapy to monotherapy with metformin (but not a sitagliptin arm). Our meta-analysis (2 trials; n=1,478) found greater reduction in HbA1c with sitagliptin 100 mg plus metformin 2,000 mg over 18 to 24 weeks compared with metformin monotherapy (WMD −0.60%, 95% CI −0.75 to −0.45). Greater reduction in HbA1c with dual therapy with metformin and sitagliptin than with component monotherapy in a 24-week trial with additional 30 and 52 week extensions (range 0.4% to 1.2%).
Low	Two trials found no difference in weight reduction between sitagliptin plus metformin and component monotherapy. In 1 trial, sitagliptin plus metformin was associated with greater weight loss than metformin alone at 18 weeks (between-group difference −1.6 kg, 95% CI −2.1 to −1.1). The second trial found a similar reduction in weight with both dosages of sitagliptin plus metformin (−0.7 kg to −1.7 kg), metformin monotherapy (−1.0 kg to −1.7 kg), and sitagliptin (−0.8 kg) over 26 weeks.
Low	Gastrointestinal events were reported with similar frequency across treatment arms in both trials, with the higher-dose metformin monotherapy patients reporting the highest rates. Our meta-analyses of 2 trials comparing the combination of sitagliptin 50 mg plus metformin 1,000 mg twice daily with monotherapy of metformin 1,000 mg twice daily found a significant difference in favor of combination therapy for diarrhea outcomes (RR 0.74, 95% CI 0.58 to 0.95). Meta-analyses for hypoglycemia (RR 1.75, 95% CI 0.50 to 6.10), nausea (RR 0.83, 95% CI 0.57 to 1.22), and vomiting (RR 1.39, 95% CI 0.62 to 3.13) were not statistically significant.
Fixed-dose combination products or dual-therapy: Invokamet® or dual therapy with canagliflozin plus metformin	
Low	One trial (n=1,186) of canagliflozin plus metformin compared to component monotherapy found that dual therapy was superior in mean reduction in HbA1c (canagliflozin 100 mg plus metformin vs. metformin: treatment difference −0.46%, 95% CI −0.66% to −0.27%; canagliflozin 300 mg plus metformin vs. metformin: treatment difference −0.48%, 95% CI −0.67% to −0.28%; canagliflozin 100 mg plus metformin vs. canagliflozin 100 mg: treatment difference −0.40%, 95% CI −0.59% to −0.21%; canagliflozin 300 mg plus metformin vs. canagliflozin 300 mg: treatment difference −0.36%, 95% CI −0.56% to −0.17%). The proportion of patients achieving an HbA1c <7% was significantly greater in the higher dose of dual therapy compared to metformin (56.8% vs. 43.0%; RR 1.32, 95% CI 1.10 to 1.59) but not for the lower dose of dual therapy (49.6% vs. 43%; RR 1.16, 95% CI 0.95 to 1.41); dual therapy superior to canagliflozin monotherapy at canagliflozin doses of 100 mg (49.6% vs. 38.8%; RR 1.28, 95% CI 1.05 to 1.57) and 300 mg (56.8% vs. 42.8%; RR 1.32, 95% CI 1.11 to 1.60).
Low	Weight change was also significantly reduced with dual therapy compared to monotherapy (canagliflozin 100 mg plus metformin vs. metformin: treatment difference −1.4 kg, 95% CI −2.1 kg to −0.6 kg; canagliflozin 300 mg plus metformin vs. metformin: treatment difference −2.1 kg, 95% CI −2.9

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Strength of evidence[a]	**Conclusions**
	kg to −1.4 kg).
Insufficient	No differences in overall adverse events or withdrawal due to adverse events.
Fixed-dose combination products or dual-therapy: Glyxambi® or dual therapy with empagliflozin plus linagliptin	
Moderate	Two trials (n=667 and 686) found dual therapy with empagliflozin plus linagliptin to be superior to component monotherapy in mean reduction in HbA1c, the proportion of patients achieving HbA1c <7%, and mean weight reduction in drug-naïve patients and patients on background metformin therapy.
Low	No differences in overall adverse events or withdrawal due to adverse events.

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; OR, odds ratio; RR, relative risk; WMD, weighted mean difference; XR, extended release

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